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### MAKING DOCTORS.<sup>1</sup>

By EWEN DOWNIE, M.D., F.R.C.P., F.R.A.C.P.,  
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Melbourne.

IN order to appreciate the pattern of training of a medical student, it is necessary to look back into the past to realize how much we owe to traditions developed through centuries of man's struggle with disease. It should be obvious that this training is concerned with two principal objects: the first is the treatment of the patient himself, as an individual, the second the treatment of his disease, whatever it may be. It is interesting to reflect that the first of these objects—namely, the doctor-patient relationship—was clearly enunciated by Hippocrates two thousand years ago and has withstood the test of time. The standards and ethical behaviour of this most honourable of professions have remained unchanged through many centuries. The second object, the training of the student in the treatment of disease, has naturally altered over the years with the changing concepts of disease and disease processes. Throughout the ages medicine has sought help from magic, from astrology, from alchemy, from religion and most recently from science. These changes in alliance of medicine to contemporary philosophy have yet another aspect.

<sup>1</sup> Read at the annual meeting of the Alfred Hospital on July 9, 1953.

I refer to the fact that the medical man himself and his status in a community are altered by sociological and economic factors which themselves change slowly and without obvious disturbance. Trevelyan, in the introduction to his "English Social History", has made this statement:

On the whole social change moves like an underground river obeying its own laws or those of economic change rather than following the direction of happenings that move on the surface of life.

So the influence of the social and economic change of the present time is having a definite and not inconsiderable effect upon the teachers and teaching of medicine itself.

The doctor-patient relationship was clearly defined by Hippocrates, and it is appropriate to quote certain sections from the Hippocratic oath, which has determined the pattern of medical ethics from that time onwards:

To think of him that taught me this Art as I think of my parents, to hold my life as his life, and to give him in the time of his need a share of my belongings. To consider his sons as my brothers and to teach this Art to such of them as wish to learn it without payment or agreement. To impart the doctrine and the interpretation and the whole learning to my sons and to my master's sons and to students enrolled and sworn to medical law and to no others. I will use all ways of medical treatment that shall be for the advantage of the sufferers according to my power and judgement and will protect them from injury and injustice. And whatever in practice I see or hear or even outside practice which is not right should not be told abroad, I will be silent, counting as unsaid what was said.

These sentences embody the highest aims of medical tradition and practice, and irrespective of the changing philosophies of disease are the standards to which we subscribe at the present time. It is, I think, significant that in an era of change in the relationship of medical men to the State and to their patients, these traditions are still regarded highly and jealously guarded.

The training of the medical student has evolved slowly from the spiritualistic days, when the tribal cults of medicine were passed by word of mouth from one generation to the next, a typical form of apprenticeship. Organization of medical practice was first mentioned during the Babylonian era in the code of Hammurabi. This remarkable enactment contained strict laws relating to medical practice and imposed severe penalties upon the practitioners of unsuccessful surgery. Egyptian medicine was of a somewhat different character, being more of a craft than a religion, and three types of healers were recognized—the physician, the priest and the exorcist. The Egyptians for the first time in history made some attempt to institute rational treatment. The Greeks developed a system of medicine which excluded the transcendental attitude and was founded upon observation and reasoning. Medicine became not only a craft, but a philosophic discipline. The Greeks made two of the greatest discoveries in medical history—firstly, that disease is a natural process, and secondly, that the human body has an innate healing power which endeavours to overcome illness and to restore the lost balance of health.

When Christianity came to the world, it entered into competition with the pagan cults and promised both spiritual and physical healing. With the adoption of the Christian religion the significance of disease changed, and with it the position of the sick man in society, and also that of the doctor. The invalid was no longer regarded as an inferior being abandoned by his fellows, but came to be recognized as one to be nursed and helped. It became the duty of society to care for the poor and the sick, and these tenets have been observed throughout the Christian world to the present day.

For a time Christian doctrine and Hellenistic science were irreconcilable, and we read that in the second century Christian students of Galen were excommunicated for studying pagan medicine. Very gradually this changed, and the cultural policies of the Benedictine order came to embrace not only the care of the sick, but the study of Grecian literature, which included medical books. Thus eventually Greek rational therapy triumphed over Christian faith healing; but mediæval medicine never lost the marks of its religious origin. The earliest physicians were craftsmen and were trained through apprenticeship; their number was small and, apart from large cities, most places were served by itinerant practitioners. The physician was not licensed, and anyone could claim to be a doctor and treat patients for fees. In the latter days of the Roman Empire restrictions were made, and the numbers of doctors in each city were limited and made conditional on the production of credentials and these privileged few were entitled the "*valde docti*". By the third century A.D. the Roman State, realizing its responsibility for the training of physicians, appointed professors of medicine in Rome. Many physicians held salaried positions at court or in the army, and some were attached to families who paid them an annual fee; still others were in private practice, where competition was fierce and specialism highly developed.

The first organized medical school in Europe was founded at Salerno. It was apparently not a monastic foundation, but attempted to coordinate the teaching of medicine without restriction as to religion or nationality. It granted degrees after a period of three years' study of logic followed by five years' study of medicine and a further year of practice under supervision. Successful candidates subscribed to an oath upholding the ethical tradition of the Greeks, and they were entitled to practise, the aim being to preserve tradition and to guarantee high standards. The conditions of practice of medicine were contained in royal decrees both in Sicily and in Austria, which restricted the practice of medicine to graduates of Salerno. Later, with the foundation of western universities, those which possessed medical faculties maintained a strict control not

only of the training of doctors, but of their subsequent practice, aiming to maintain tradition, to preserve high standards of quality and to eliminate competition by strictly regulating fees. The mediæval world was a static world. Man was born with a divine mission to fulfil, and salvation, not the accumulation of wealth, was his purpose. It was an authoritarian world dominated in all its aspects by the Church. The professions were vocations implying duties both to God and to fellow men.

At the time of the Renaissance a strong trend towards realism developed, and this change coincided with the new conception of science, which from the seventeenth century onwards has developed with ever-increasing rapidity. The spirit of inquiry into the causes of disease has brought medicine under the influence of science and has given man power over Nature. In each succeeding century more natural forces have been subjugated to serve man's purpose, and the fight against disease has been conducted with scientific weapons of ever-increasing efficiency. The doctor is no longer a sorcerer or a priest or even a mere craftsman, but a man of science. Along with this there occurred another change also about the sixteenth century, in which a new economic order arose, appealing to the individual in man and calling for free initiative, free trade and free competition. Traditional authority was opposed, and the most powerful exponent of this, the Church, was "reformed". The new political philosophy of liberalism sapped the economic power of the craftsmen's guilds; but for a long time the universities refused to adapt themselves to the new conditions and adhered to mediæval forms and traditions. However, medical faculties gradually lost their power to control the practice of medicine, which in many countries was taken over by the State.

From the time of the Middle Ages the control of practice in Great Britain was largely exercised by corporate bodies, which maintained jurisdiction over a radius of certain distances from their headquarters. These bodies had the power to examine candidates and to decide who was worthy of engaging in practice. In the year 1858, with the passage of the *Medical Act* in Great Britain, there was formed the General Medical Council of Medical Education and Registration in the United Kingdom. This Act did not forbid the practice of medicine by unqualified or unregistered persons, but its object was to enable persons requiring medical aid to distinguish qualified from unqualified practitioners. The General Medical Council was required to keep a medical register of qualified persons, and was given power to require licensing bodies to furnish information as to courses of study and examinations necessary to obtain qualification. In Australia today there are four licensing bodies, all of which are universities, which train and examine their own undergraduates. The qualifications of the four Australian schools are represented to the various State registering bodies, known as medical boards. The standards of each of the Australian medical schools are such that complete reciprocity exists as to registration and ability to practise in any State of the Commonwealth, irrespective of which of the licensing bodies has granted the qualification. It has become the function of the State to act as guarantor of the standard of medical training and ethical practice; but up to the present time there has been no indication of the State's attempting to disturb the pattern of training. This is an important fact to realize, for we may be approaching an era in which State control or direction of education could be applied to the teaching of medicine.

What are the aims of medical education at the present time, and in what way are they being achieved? What part are we in the Alfred Hospital playing in the process? Not only must the making of the medical man of today be concerned with the maintenance of a high standard of professional attainment in order that the practitioner should be worthy of his calling, but his training must be such as to enable him to appreciate the enormous influence which science is wielding on everyday life and on medical thought. The training of doctors has always been based on apprenticeship. In hospital wards, in out-patient departments and in the home, medicine has been taught by practising physicians, and herein lies the learning of the

art of medicine. In bygone times the apprenticeship was served with one master, who perhaps for some years was entirely responsible for a student's training. Now a large number of highly specialized teachers is concerned with any one student. In consequence it is hard to say how far any present teaching succeeds in the difficult task of cultivating the art and science simultaneously. On the one hand criticism comes from experienced practitioners who complain that there is not enough instruction in common diseases, while on the other hand many examiners and specialists say that students do not gain enough grasp of principles to enable them to handle unfamiliar situations or to think critically. However, one point of unanimity exists in any body of teachers concerned with medical education: they all agree that, irrespective of any other consideration, their own particular subject is of such importance that more time should be devoted to it during the course.

I have little doubt that there is a dangerous trend at present to devote too much time to too specialized instruction, both in the basic subjects and in clinical teaching. On the other hand, too little time is allowed for a student to digest, let alone assimilate, the vast amount of highly specialized information which is presented to him. Science teaches facts; but science does not teach how to discriminate between facts or how to use them, and many teachers seem to have neither the time nor the ability to be concerned with this problem. The authoritarian pattern of medical education of the Middle Ages is now replaced by a specialized and incoordinated curriculum vainly seeking to produce a result in somewhat less time than was thought necessary by the school of Salerno over a thousand years ago. Admittedly the response of the medical profession to the wealth of scientific knowledge has been a greater and greater specialization in practice, and the training of a true specialist of necessity proceeds for many years after graduation. Nevertheless, surely the primary function of medical schools is the education of undergraduates and the fashioning of a man who is capable of caring for the diseased person, who is aware of his limitations, who has sufficient training to be able to appreciate advances in knowledge, and who is sufficiently prepared so as to be capable of proceeding along any specialized lines of study and practice should he so desire.

In all this modern thirst for knowledge there is a tendency to forget the patient, and I should like to quote a short paragraph from an address given by Sir Robert Hutchison a few years ago:

Medicine in practice is not yet so scientific as many like to pretend. Indeed it is only comparatively recently that it has even been described as a science. Hippocrates always spoke of the Art and the same is true of all medical writers after him down to quite modern times. But one of the tendencies of the present day is to exaggerate the scientificness (if I may use the term) of Medicine. In the first place it is responsible for the cluttering up of medical curriculums with all sorts of ologies, most of which the student forgets as soon as he has passed the examinations in them. This leads to much waste of time, for as Samuel Butler said with much truth "the physician's physiology has much the same relation to his power of healing as a cleric's divinity has to his power of influencing conduct". Last and worst, the ultra scientific outlook leads to a wrong attitude to our work at the bedside. As Sir Auckland Geddes has put it, "so many come to the sick room thinking of themselves as men of science fighting disease and not as healers with a little knowledge helping nature to get a sick man well".

Although I do not wish to be deliberately provocative, a further danger confronts the doctor-patient relationship. It is that under the nationalized practice of medicine practitioners themselves may, by the very nature of their contract with the State, fall into the habit of being over-bureaucratic as well as over-scientific in their handling of disease and in the process may forget the patient.

The impact of the scientific revolution on medicine has resulted in a completely changed conception of disease and of the processes of disease. Furthermore, by the provision of highly technical instruments and laboratory techniques it has greatly improved the methods of recognizing disease.

Also, by supplying powerful therapeutic agents it has made possible the cure or the alleviation of many illnesses which even a few years ago proved to be inevitably fatal. For these advances medicine and the human race owe much to scientific technology. The debt does not end here, for the investigation and treatment of many diseases now involve complicated procedures and drugs, the cost of which is reaching such alarming proportions as to necessitate radical changes in the methods of financing hospital and medical care. The alliance of medicine and science has proved beneficial but expensive.

What now of the medical student of today? In what way is he to be trained to take his place in the community with due regard to the various responsibilities he has to shoulder on qualification? In the early years of his medical course he is instructed in the basic subjects of biology, physics, chemistry, physiology, anatomy and biochemistry. These serve as a firm basis for the development of his subsequent knowledge; but it must be appreciated that in the first years of his course the medical student has no personal contact either with illness or with a patient. At the stage when he is received into a hospital he possesses a considerable amount of basic knowledge, but none of human beings. During his hospital course, which extends over three years, not only is the student taught the patterns and effects of disease on the human being, but he is also taught a number of other things. These include a knowledge of human beings and the management of illness under varying circumstances. Of necessity his training must take place in a hospital where at any time numerous examples of severe diseases are to be seen. It is here that he learns to develop his powers of observation, of deduction and of the weighing of evidence as to a patient's illness. He becomes familiar with the various methods of investigation which are applied to difficult diagnostic problems. He also becomes aware of the methods of treatment which are applicable to various disease states. A moment's reflection, however, will remind you of the fact that this indeed is only part of his training. The student gains his first contact with a patient when he is allowed the interrogation and examination of the patient and the supervision of treatment under the direction of members of the teaching staff. This, however, gives him little knowledge of the minor types of illness, or in fact of the treatment of illness in its natural environment—the patient's home.

It has been the considered policy of the Alfred Hospital Clinical School in recent years to endeavour to provide training over and above the basic requirements of the university curriculum. In the Annual Report you will find a brief reference to some of these activities. Any clinical school concerned with the training of medical students should be concerned with the general standard of the training provided for all students, and with the quality of all of its graduates from the highest to the lowest. It is our proud contention that an Alfred Hospital student is so trained as to be able to be recognized as such in the community, and that he can take his place alongside the best products of any other school in this Commonwealth or in the Empire. Emphasis has always been placed upon practical training. For example, before the last war it was thought that some knowledge of elementary nursing procedures should be given to all students. The value of this training was soon recognized, and now each year groups of students, under direction of the tutor sisters of the nurses' training school, engage in a course similar to that which was given to Army Medical Corps orderlies during the war. In this course all appropriate nursing procedures not only are demonstrated to the students but are practised by them. In the fourth year of the course the students are sent out with the visiting sisters of the Melbourne District Nursing Society to see the problems of chronic illness in the home, this being their first experience of sickness outside the hospital environment. Some three years ago, with the wholehearted support of the Alfred Hospital Old Residents' Association, an outstanding contribution was made to the training of students in offering them, on a voluntary basis, the chance of acting as observers in general practice. This development was

closely surveyed by *questionnaires* and has proved to be of great benefit to students, 100% of whom have voluntarily participated in the scheme both in 1952 and in 1953. I am convinced that the experience gained by the students during this fortnight is worth more to them than any other two weeks' study throughout the whole of their course. It presents to them, at a most impressionable stage, the problems of the practice of medicine in a fashion which cannot be taught in any other way.

In continuation of the policy of broadening the students' experience we have, in the past twelve months, arranged for them to participate in the routine examination of large groups of children visiting the Lord Mayor's Camp. This offers for the first time an experience in examining apparently healthy children in an attempt to detect the earliest evidences of abnormalities, if not of disease. Also this year, for the first time, with the wholehearted support of the directors of a large industrial organization, we have been able to send students to an industrial medical clinic, where they have been able to see the fitting of men to jobs in industry according to their physical and mental capacities. This has also provided an opportunity for them to see how industrial workers are cared for while at work. These adventures in the training of medical students have proved their worth and have had the effect of widening the students' outlook and of giving them a greater preparation for the tasks which confront them on graduation.

It is now appropriate to refer to the responsibilities of those who are actually engaged in the teaching of medical students. In the first three years of the course this responsibility falls on the whole-time academic staff of various departments in the University of Melbourne. During the hospital years the responsibility for teaching falls on the part-time activities of the members of the honorary medical staffs of the teaching hospitals. Appointment to such a position involves an obligation not only to treat patients admitted under one's care, but also to teach medical students attached to the hospital. The latter responsibility is an onerous and honourable task, a burden freely borne by generations of medical men brought up in the high traditions of British medicine. The present status of graduates in medicine of the University of Melbourne ranks high in the world, and is a striking tribute to the worth of our predecessors, who laid the foundations and established the traditions to which we still subscribe. However, there is in the division between university and hospital education in the earlier and later years of the course a considerable gap, as there is no close liaison between these two phases of teaching. Prior to the last war no attempt at coordination or supervision over the work in the teaching hospitals was even attempted by the university. In 1947 the late Sir Alan Newton, then Stewart Lecturer in Surgery, realizing this deficiency, formed a Department of Clinical Studies, and for the first time interested the university in its clinical schools. Sir Alan Newton assumed the position of Director of this newly formed department, and in an incredibly short space of time set to work to coordinate not only the teaching as between preclinical and clinical years, but also the standards of teaching as between the hospitals themselves. Unfortunately his falling health prevented him from realizing his ambitions; but within the short period of eighteen months he had convinced the University Council of the necessity of providing assistance to the clinical schools by the appointment of whole-time student supervisors at a cost of approximately £12,000 *per annum*. Like all pioneers, his work was not without its difficulties, and it is unfortunate indeed that the position of Director of Clinical Studies has since been abolished—a step which, to say the least of it, appears to have been a retrograde one.

At his instigation, in the year 1948 the University Council approved in principle the formation of Departments of Medicine and Surgery, thus attempting to repair a notable omission in the medical education in this State, as there is as yet no professor in either of the major subjects of medicine or surgery in this University. Lacking his inspiration and leadership, four more years were to pass before the details of this proposal were finally agreed upon at the end of 1952. It has now been accepted in

principle that there will ultimately be a professor in each subject in each of the major clinical schools. Over all the discussions on this development has hung the dreadful word "finance", the mention of which, to my own knowledge, was sufficient to cause all discussions on chairs of medicine and surgery to be abandoned in 1936. It seems appropriate to remind you of the fact that medical education, like medical treatment in the large public hospitals, is one of the things which has perhaps been taken for granted for too long. Appointment to honorary medical service in a hospital dates back to an age when medical men were prepared to give their services to the poor and to the sick who could not afford treatment in other ways. In the present economic circumstances the medical profession seems to have become a victim of its own ideals, and its adjustment to changing conditions is not an easy one.

The honorary physicians and surgeons of the teaching hospitals, the backbone of medical education in this State, are much involved in this. It is not the place here to refer to the enormous value of services given gratuitously in treatment which are now regarded as a right by anyone who gains admission to a public hospital; but I should like to indicate the value of the services given in teaching as something which few people realize or wish to recognize. At a conservative estimate the teaching of the subjects of medicine and surgery, and I do not include obstetrics, paediatrics or other specialties, would represent approximately £60,000 *per annum* if the teaching of these subjects was paid for at £3 3s. *per hour*. Such fees as are paid by students for this teaching and passed to the hospital staffs do not represent 10% of this figure. To my personal knowledge the honorary medical staffs of the hospitals at no stage have even raised a voice suggesting that their services should be remunerated on such a scale. However, it does seem somewhat galling that when these very members of hospital staffs press, as they have done, for the establishment of departments of medicine and surgery, they are frustrated by the suggestion that sums of money certainly no greater than those represented by their own services are quite beyond the capacity of university finance to provide.

In no other faculty has the University been indebted to so many for so much. It is quite obvious that funds for this development must come from the State. We have long since passed the age when private sources can possibly hope to provide appropriate endowments. Not so long ago I was a member of a committee which was called upon to cost the total charge of this proposal in its fully developed phase. Having reached a figure of £80,000 *per annum* as a not excessive estimate, I was ridiculed for suggesting such a sum. The answer to such an attitude surely is that until the value of the work which has been done over the years by the part-time staffs is known and appreciated, and until some vision and enterprise are shown in the development of the Melbourne Medical School, the request for appropriate funds will not be made and the Melbourne Medical School will decline.

In the meantime the medical profession is slowly being adjusted to the altered economic circumstances of our times. If such facts as these are not brought to public notice, the "taken for granted" attitude of honorary medical service in treating and teaching will be perpetuated to a stage at which it will threaten and undermine the whole structure of treatment and teaching in this country, for little heed will be paid to pleas if and when nationalization of the medical profession occurs. Already in Great Britain there are fears that, as a result of the nationalization of medical service, there is evidence of declining medical standards of practice and of education. Tradition is hardly earned over many generations and can be rapidly destroyed. It would indeed be a tragedy of first moment if, in the process of creation of a welfare State, the welfare of the State from the medical point of view was to be destroyed.

The student of today, as he is a human being, like all others, is concerned with security of tenure and of his future. In an individualistic profession such as that of medicine, this is a dangerous attitude, tending as it does to destroy initiative and denying the incentive to post-

graduate knowledge and advancement. The teachers of medicine today have not only to keep abreast of the most recent scientific advances, but they have also to keep abreast of the changing attitude of the times. Too little heed is being paid at the present time to the possible influences of economic and social change upon the pattern of medical education and medical practice of the future. If the profession be engulged in self-interest in hours, security and tenure, then the doctor-patient relationship will be threatened and the individual members of the community must suffer.

The time is surely opportune for some detached and authoritative body, similar to the Goodenough Committee which was set up in Britain in 1942, to examine the problems of medical education throughout Australia, and to make such recommendations as seem appropriate to safeguard the standards of teaching in the Commonwealth. This is neither the time nor the place to engage in any detailed consideration of this suggestion; but without some well-defined policy and clear leadership the proud heritage in our possession may well be lost. In conclusion, let me quote a distinguished physician, Edouard Rist, who taught me much, and whose words express my feelings better than I could do myself:

To be a good doctor, you must love Medicine. You cannot love it well unless you love also those who have brought it to where it is today. Then you realise that in doing your best, you are but paying a debt.

#### REPORT ON "MYSOLINE" IN THE TREATMENT OF MENTAL HOSPITAL EPILEPTICS.

By B. G. BURTON-BRADLEY,  
Brisbane Mental Hospital, Queensland.

"MYSOLINE", a new drug in the treatment of epilepsy, was synthesized by Bogue and Carrington in 1949, who also showed that it protected laboratory animals against electrically or chemically induced convulsions, and had extremely low toxicity. It is stated that, though related to phenobarbitone, "Mysoline" is of a chemical type not previously used in man.

Its formula is 5-phenyl-5-ethyl-hexahydropyrimidine-4:6-dione (Figure I).

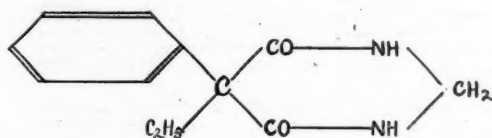


FIGURE I.

Handley and Stewart (1952) showed that "Mysoline" greatly reduced the number and severity of fits in their series of 40 cases, and that it was without serious toxic effects, and could be used in all types of practice without laboratory control.

At the Brisbane Mental Hospital 18 mental hospital patients were treated over an average period of four months. All patients were known to have had major convulsions; all had either an associated psychosis, or behaviour of such a character as to have warranted commitment procedures. Five had associated amentia, one of whom was an *idiot savant*. The epilepsy of the rest was regarded as of idiopathic type. All the patients had been previously treated with "Dilantin" and phenobarbitone. The criteria of selection were the greatest number of residual fits under the previous treatment, and the cooperation of the patient in a new form of treatment, whenever this could be obtained by virtue of his understanding. At

the commencement of treatment there were 161 epileptics in the hospital, in a total hospital population of 2500. It was concluded that the patients treated were among the most disabled epileptic members of the Queensland community.

No attempt was made to extinguish seizures entirely, as this is not the design in treatment, and may leave the patient stupid and unhappy (Lennox, 1951). No patient received more than 1.25 grammes of "Mysoline" daily. Major fits and behaviour were recorded, and compared with the patients' previous record. Records for twenty-four hours of each day were obtained; the charge nurse responsible for the patient decided the nature of the fit, and recorded *grand mal* attacks only. "Benefit" in behaviour as used here refers to a quality not previously present. Its components include spontaneous performance of new tasks, aesthetic interests, amenities, interest in appearance and ward behaviour.

"Mysoline" is supplied in tablets of 0.25 gramme each, and starting with one tablet on the first day it was gradually introduced over a period of ten to twelve days, during which time the previous treatment was gradually abolished. At the end of this period, patients were receiving 0.5 gramme twice a day. In a few cases in which the fits did not seem to be adequately controlled, the dosage was increased to 1.25 grammes a day. Handley and Stewart consider that the flexibility of dosage ranges from 0.75 to 2.0 grammes per day. Eight of the patients were given "Dilantin", 1.5 grains three times a day, in addition to "Mysoline".

#### Results.

The results are recorded in Tables I and II. Except in one case, in which "Dilantin" was being given in addition to "Mysoline", the anticonvulsive properties of "Mysoline" were as good as, and in most cases better than, those associated with previous forms of treatment. Had the dosage been increased, no doubt the results in this regard would have been even better.

Except in Case XVIII, in which the patient became confused, and her behaviour became so violent that it was decided to suspend the treatment after fifty days, the behaviour of the rest of the patients was no worse and in nine cases was very much better. This may have been due to enthusiasm for a new treatment, but it is interesting to note that the benefit was still present at the end of the treatment period. The combination of "Mysoline" with "Dilantin" did not appear to be superior to "Mysoline" alone (see Tables I and II). The following cases are of some interest.

CASE VIII.—This female patient, aged sixty-five years, had a long history of violent behaviour. She was often described as "bad tempered and morose". She used bad language frequently. She exhibited the features of the so-called epileptic personality, egotism, rigidity, moodiness and perseveration. Since the establishment of "Mysoline" therapy, she is polite and considerate, and has ceased to pursue the medical officers with demands for her discharge from hospital, which has been her usual custom for years.

CASE XIII.—This boy, aged twenty-two years, has had major convulsions since the age of eleven years. He has spent most of his time since the age of sixteen years in a mental hospital. His records show a long consistent history of violent behaviour. He had threatened to kill his father, and is alleged to have attempted to strangle a child. A considerable portion of his violent behaviour was of the complex, prolonged, premeditated variety, so would not be due to epileptic discharge as such, according to Denis Williams (1953). During the four months' treatment period his conduct has been excellent, unlike anything previously, and he has shown no traces of aggressiveness and has worked well at gardening. His ambition now is to learn a trade. Improvement is still present.

CASE XVI.—This female patient, aged forty-nine years, has commenced working in the ward for the first time since her admission to hospital twelve months ago. In addition she has spontaneously taken an interest in drawing, and, although her efforts do not appear to have any great artistic merit, they reveal a desire to create. Formerly noisy each night, she now sleeps without sedatives.

TABLE I.  
"Mysoline" and "Dilantin".

Case Number.	Sex.	Age. (Years.)	Daily Dosage of "Mysoline" and "Dilantin". <sup>1</sup>	Days of Treatment.	Previous Average Incidence of Fits Over Four Months.	Fits During Treatment.	Percentage Reduction of Fits or Otherwise.	Behaviour.
I	M.	44	D., one capsule three times a day. M., two tablets twice a day.	125	0	1	Worse	Unchanged.
II	M.	22	D., one capsule three times a day. M., two tablets twice a day.	127	11	1	91	Unchanged.
III	M.	43	D., one capsule three times a day. M., two tablets twice a day.	127	0	0	0	Benefit.
IV	M.	37	D., one capsule three times a day. M., two tablets twice a day.	127	1	0	100	Benefit.
V	M.	30	D., one capsule three times a day. M., two tablets twice a day.	126	1	1	0	Unchanged.
VI	F.	43	D., one capsule three times a day. M., two tablets twice a day.	125	1	0	100	Unchanged.
VII	F.	45	D., one capsule three times a day. M., two tablets twice a day.	125	2	0	100	Benefit.
VIII	F.	65	D., one capsule three times a day. M., two tablets twice a day.	127	0	0	0	Benefit.

<sup>1</sup> "M" = "Mysoline", 0.25 gramme; "D." = "Dilantin", 1.5 grains.TABLE II.  
"Mysoline" Only.

Case Number.	Sex.	Age. (Years.)	Daily Dosage of "Mysoline" <sup>1</sup>	Days of Treatment.	Previous Average Incidence of Fits Over Four Months.	Fits During Treatment.	Percentage Reduction of Fits.	Behaviour.
IX	M.	29	Three tablets in morning. Two tablets at night.	132	33	24	21	Unchanged.
X	M.	31	Three tablets in morning. Two tablets at night.	132	15	7	53	Unchanged.
XI	M.	28	Two tablets in morning. Three tablets at night.	127	6	4	33	Unchanged.
XII	M.	30	Two tablets twice a day.	128	0	0	0	Benefit.
XIII	M.	22	Two tablets twice a day.	127	1	1	0	Benefit.
XIV	M.	38	Two tablets in morning. Three tablets at night.	128	0	0	0	Benefit.
XV	M.	48	Two tablets twice a day.	125	5	5	0	Benefit.
XVI	F.	49	Two tablets twice a day.	127	7	0	100	Benefit.
XVII	F.	35	Two tablets twice a day.	101	Unknown	3	Unknown	Unchanged.
XVIII	F.	37	Two tablets twice a day.	50	1	0	100	Worse.

<sup>1</sup> 0.25 gramme.

#### Side Effects.

With the dosage used, side effects were few and transient. Two patients developed nystagmus, drowsiness and a drunken gait on the first day of treatment, a few hours after receiving only one tablet of "Mysoline" (0.25 gramme). These symptoms disappeared the following day, and did not return, and treatment was not stopped on account of this. One of these patients said that she had had the same symptoms when she originally commenced "Dilantin" therapy. One patient became drowsy on the tenth day, and slept for two hours in the afternoon. One patient became confused and violent during the sixth week, and treatment was suspended. Regular clinical examination revealed no other symptoms or signs during the course of treatment. Drug rash was not observed. Blood counts (haemoglobin estimation, total and differential white cell counts) and urine examinations revealed no abnormality.

#### Summary.

1. "Mysoline" treatment of 18 mental hospital epileptics is described.

2. Over a four months' period the anticonvulsive properties of "Mysoline" were found to be better than (nine cases), as good as (eight cases), and worse than (one case) those of previous forms of treatment.

3. An improvement in behaviour is noted in nine cases.

#### Acknowledgements.

I wish to express my thanks to Dr. B. Stafford, Director of Mental Hygiene, and Dr. C. R. Boyce, Medical Superintendent, Brisbane Mental Hospital, for allowing the investigation to be carried out, and to Imperial Chemical Industries of Australia and New Zealand, Limited, for the supply of "Mysoline" tablets.

#### References.

- HANDLEY, R., and STEWART, A. S. R. (1952), "Mysoline: A New Drug in the Treatment of Epilepsy", *Lancet*, 1: 742.  
 LENNOX, W. G. (1951), "Control of Seizures with Drugs", in "Modern Medicine".  
 WILLIAMS, D. (1953), "Phenomena of Epilepsy", *Brit. M. J.*, 1: 173.

**"MYSOLINE"—ITS USE IN EPILEPSY.**

By JOHN A. GAME,

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Melbourne.

THE first clinical report of the use of "Mysoline" (5-phenyl-5-ethyl-hexahydropyrimidine-4:6-dione) (Handley and Stewart, 1952) was most encouraging.

As this report was confined to experience in an epileptic colony, it was decided, with the cooperation of Imperial Chemical (Pharmaceuticals) Limited, to try to reach an evaluation of the drug when used for hospital out-patients over a six months' period. The limitations of such a short-term evaluation were fully appreciated from the outset; but the importance of the original claims seemed to warrant the early appraisal and report of any experience which appeared to modify them.

**Materials and Method.**

It was decided to select for trial 20 patients whose epilepsy was not being controlled effectively with various combinations of anti-convulsants in current use. They were in effect our 20 most difficult patients. They all suffer *grand mal* and various forms of lesser attacks, including focal motor or sensory attacks, other minor attacks having the signal of focal origin such as temporal lobe epilepsy, and the more classical *petit mal*. In most cases the existence of some structural abnormality of the brain is suspected, and in many it has been demonstrated by air encephalography or angiography. These abnormalities include dilatation of the ventricles, either confined to one region or uniform throughout their extent, *angioma cerebri* and Sturges-Weber syndrome.

The patients vary in intelligence from well above average to mild degrees of mental defect, and their personalities cover an equally wide range. Their ages are scattered between nine and fifty-three years, and they have been subject to epileptic attacks for periods varying from six months to twenty years, the average being approximately twelve years.

The frequency of attacks in individual patients at the time when the trial began varied from the occurrence of one per month to several major attacks per day. Some years ago one of the patients had had a period of six months' freedom from attacks; but the majority had never enjoyed anything like as long a respite.

The method of introducing the drug was that suggested by Handley and Stewart (1952), but for reasons to be stated below, this has drawbacks. While they were still taking their previous treatment, the patients were given 0.25 gramme of "Mysoline" twice a day. On each fourth day thereafter the dose of "Mysoline" was increased by one tablet until four, five or six tablets were being taken daily (in divided doses twice or three times a day before meals).

Beginning from the end of the first or second week, the dosage of the previous medicine (in most instances phenobarbitone, sodium-5-5 diphenylhydantoinate and/or 3-methyl-5-phenyl-5 ethyl-hydantoin (methoin)) was reduced by one tablet or capsule *per diem* until it was totally eliminated; usually the phenobarbitone was reduced first, then the sodium diphenylhydantoinate, and finally the methoin.

Each patient was given a small note book, and asked to record on the left side page the number of attacks, and on the right hand page how he felt, the records to be made daily. The patients attended the neurological out-patient department weekly at first, and as their dosage became established the visits were gradually extended to once a month.

At each visit a note was made of their recorded number of seizures and their well-being, and of one's personal evaluation of their clinical state and subjective impressions, with special attention to side effects.

It is necessary here to state one's impressions of the limitations of the strictly statistical method of evaluating anti-convulsant drugs. Many of our patients hold gainful employment, and they all live in their own homes. In this respect they are far more representative of the large mass of epileptic people than those who live in epileptic colonies. Such people demand more than mere suppression of their attacks; they must have also the physical vigour and mental alertness to do their jobs. Therefore, any assessment of a drug based purely on the statistical analysis of the number of attacks can tell only half the story. Furthermore, one's experience in both hospital out-patient and private practice leads one to doubt whether any such assessment can be made with even reasonable accuracy. Patients and their relatives can seldom make reliable records by any method. Many attacks pass unnoticed; what one patient ignores as a "feeling" or warning another calls an attack, and what are called "big" attacks by some and "small" attacks by others is anybody's business. Seldom, however, will patients or relatives fail to tell one at their regular visits whether they have been "better" or "worse" since their last visit. Their testimony as to whether they are now better or worse than six or twelve months ago is far less reliable. Therefore, an attempt has been made to assess this from past records and by cross-questioning of the patients in the light of these records. It is thought that a good deal of reliance can be placed upon patients' stated preference for this or that drug or combination of drugs.

As an independent check we have had most of the patients, and when possible their relatives, interviewed by a medical social worker attached to the clinic, and her assessment has been recorded separately; for various reasons such interviews could not be arranged in three instances.

All patients in the series have had a full neurological examination, an X-ray examination of the cranium and chest and an electroencephalographic examination, and most have at some time been in the wards for full investigation by air encephalography and, where indicated, percutaneous carotid angiography. As the series is obviously too small to relate results of treatment to any pathological grouping of patients, those details will not be recorded, but are available for inspection.

**Side Effects.**

Drowsiness and drunkenness were the rule rather than the exception during the first few weeks (Table I). Obviously, this was to some extent due to the continued intake of previous drugs in addition to "Mysoline" during the initial stages of treatment; as will be shown, different methods of introducing the drug are necessary.

Of particular interest was the individual variation in susceptibility to these side effects. Whilst the majority of the patients, taking two tablets of "Mysoline" *per diem* in addition to their previous medicine, were almost amusingly drunken (women and children too), one young man consistently reported a feeling of "liveliness and amazing energy" and looked well, and others were only a little affected. One woman of higher intelligence and unusual activity has been consistently pleased with the drug because, despite more drowsiness than formerly, she is conscious of a much greater sense of well-being.

At the other extreme, one patient had to be admitted to hospital.

R.G., a male patient, aged twenty-seven years, is suffering from post-traumatic epilepsy. On the tenth day of "Mysoline" therapy his vision was blurred, his speech was thick and he was sleeping excessively. He was admitted to hospital on the fourteenth day. He was "dopy", had half-closed bleary eyes and could not stand or walk without falling, and his speech was unintelligible. Apart from his ataxia and depressed consciousness, no other objective neurological signs were detected. The administration of "Mysoline", 1.0 gramme *per diem*, was continued, but all other drugs were withdrawn. After twelve days the patient was vastly improved and discharged to his home. At his worst stage an electroencephalographic examination revealed diffuse slow activity (not sleep rhythm), whereas earlier and later

records were normal. A full blood count, cerebro-spinal fluid examination, an electrocardiographic examination and a microscopic examination of the urine all gave normal results.

With further experience one's opinion now is that "Mysoline" can be taken by the majority of people without serious inconvenience from its side effects, if modified methods of introduction and gradual increase to the recommended dosage are followed.

It is now the practice to begin with one tablet taken at night time in lieu of part or whole of the evening dose of other drugs which the patient is taking. This is continued for two weeks. This procedure has been adopted because one's past experience has confirmed the observation of Handley and Stewart (1952) that the initial symptoms of drowsiness and drunkenness tend to disappear as the patient becomes accustomed to the drug. Although the period of action of an individual dose is unknown, the

Some impressions of the value of "Mysoline" have already been implied in the discussion of side effects, and experience is providing a firmer opinion and knowledge of the use and limitations of this drug.

Tabulation of our results (Table II) suggests that most patients can be maintained on "Mysoline" alone, as well as they have been in the past by the combination of other drugs. Some, perhaps about half, are better maintained, and of these a few are very much better controlled.

In the five instances of discontinuance of the drug, this was mainly the result of the patient's temperamental or personal unsuitability for cooperation in a trial of this nature. In no instance was the patient's epilepsy definitely worse, nor was the abandonment due to severe side effects. Those who experienced the worst side effects valiantly carried on, and thanks are due to them.

TABLE I.

Condition.	Number of Cases.
Improved alertness from beginning ..	1
No change .. .. .	5
Slight initial confusion or drowsiness ..	6
Staggering gait, drawing speech and sleepy	4
Very drunk, unable to walk, talk or feed	3
Inconclusive assessment due to alcoholism and temperament .. .. .	1
Total .. .. .	20

manufacturers, through Dr. L. B. Wevill (private communication), have advised that they consider the maximal effect to be about four hours after administration. The object is to enable the patient to become accustomed to the drug during his normal sleeping period and so to suffer no inconvenience during his waking hours. The patients comment that they enjoy better sleep during this initial period.

From this point, it is now the practice to increase the dose of "Mysoline" by one tablet per week with reduction of the dose of phenobarbitone or phemitone *pari passu*. The dose of sodium diphenylhydantoinate is now left unaltered, as there seems little doubt that the most effective routine use of "Mysoline" will be in combination with sodium diphenylhydantoinate.

By the use of these methods the early side effects have been much reduced, but not eliminated. However, one feels more confidence in encouraging the patients during this phase and in assuring them of their ultimate improvement.

Once the patients are past this initial stage, the recurrence of the side effects with increase in dosage may become a problem. One's current experience is that four or sometimes five or six 0.25 gramme tablets of "Mysoline" *per diem* are the optimum, when combined with sodium diphenylhydantoinate. With larger doses drowsiness and unsteadiness tend to reappear.

There has been no instance of any dangerous metabolic toxic effects from taking "Mysoline".

It is encouraging to speculate how effective this non-toxic drug could be if the inconvenient side effects did not prevent the use of larger doses, and one hopes that the chemists will soon achieve a suitable modification.

#### Results.

As the object of the trial was to assess the value of "Mysoline" as an anti-convulsant drug in humans under normal clinical conditions, it was not combined with other drugs during this initial six months' period of trial.

No statistical statement of the results could be made from so small a series; nor, for reasons already given, is such a statement considered necessarily reliable in revealing the true value of an anti-convulsant drug.

TABLE II.

Effects of "Mysoline".	Medical Assessment. (Number of Patients.)	Almoner's Assessment. (Number of Patients.)
Improved +++ (no attacks) .. ..	1	1
Improved ++ .. .. .	1	3
Improved + .. .. .	7	6
No change .. .. .	6	2
Unclassifiable .. .. .	Nil	3 <sup>1</sup>
Worse .. .. .	Nil	Nil
Drug discontinued .. .. .	5	5
Total .. .. .	20	20

<sup>1</sup> Not interviewed by almoner.

Since the completion of the six months' period of trial with "Mysoline" alone, sodium phenylhydantoinate has been added in many cases, and there are indications that more can be expected from this combination than from the use of "Mysoline" alone. A further prolonged period of observation will be necessary before any conclusions can be drawn.

#### Discussion.

Reference has already been made in earlier paragraphs to various aspects of the problem.

The number of patients and the length of experience are both too small to allow lasting conclusions to be formed. The constant appeal of those afflicted with epilepsy for better control of their disorder seems ample justification for the publication of early impressions of a new drug for which much has already been claimed. The fact that one's impressions are that "Mysoline" is a drug worthy of serious consideration for a place in the treatment of these patients, seems a further reason for the publication of impressions and experience which may help others to save time and avoid difficulties in the introductory phase, and so reach valid conclusions earlier.

#### Summary.

The experiences and impressions of the use of "Mysoline" alone, in substitution for drugs in current use, gained in the treatment of 20 severely epileptic patients in a neurological out-patient department for a period of six months, are discussed.

No patients became worse, and about half were improved, some considerably so, and one becoming completely free of seizures.

The treatment was accompanied in many cases by initial side effects of considerable and incapacitating degree, but no dangerous metabolic toxic effects were observed.

Suggested modifications of method and dosage in the introductory phase are expected to diminish these side effects to practical proportions, and so widen the scope of usefulness of the drug.

Subsequent observations suggest that the combination of "Mysoline" and sodium diphenylhydantoinate may produce better results than "Mysoline" alone.

#### Reference.

HANDLEY, R., and STEWART, A. S. R. (1952), "Mysoline: A New Drug in the Treatment of Epilepsy", *Lancet*, 1:742.

### "MYSOLINE":<sup>1</sup> A CLINICAL EVALUATION OF A NEW DRUG IN THE TREATMENT OF REFRACTORY CASES OF EPILEPSY.

By GEORGE SELBY.

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DURING the past fifteen years several good anti-convulsants have become available and have enabled us to reduce the frequency of fits and make life tolerable for the majority of our epileptic patients. There remains, however, a hard core of epileptics who are resistant to all our therapeutic efforts, and the search for more efficient drugs to inhibit convulsions continues.

In 1949, Bogue and Carrington (1953) found a new anti-convulsant drug now known as "Mysoline". Laboratory tests proved this new compound of extremely low toxicity, both acute and chronic, and showed that its anti-convulsant potency compared favourably with that of all other drugs used in the treatment of epilepsy, when the effective dose was considered in relation to the toxic dose.

"Mysoline" may be considered as a derivative of phenobarbitone in which the oxygen in the urea grouping of the barbituric acid is replaced by two atoms of hydrogen. Its chemical name is 5-phenyl-5-ethyl-hexahydropyrimidine-4:6-dione.

The first clinical trial was carried out by Handley and Stewart in England and was published in April, 1952. They reported cessation of seizures in 30%, and improvement in a further 47.5% of 40 chronic epileptics with mainly *grand mal* seizures, over a trial period of six months. No changes in the blood, renal damage or other serious toxic effects were noted.

More recent reports have come from Canada, where Smith and McNaughton (1953) observed a reduction of 50% or more in the fit incidence of 23 out of 51 epileptics who had taken "Mysoline" for from four to sixteen months. They mention also lessening in psycho-motor seizures in four patients with an electroencephalographic focus in the temporal lobe. In their total series of 66 cases, treatment had to be discontinued within six weeks in 10 patients, five of whom exhibited psychiatric manifestations. Another seven of their patients had transient minor emotional disturbances, which ceased in spite of continuation of therapy. Again no toxic damage to the marrow or kidneys was found.

Bonkalo and Arthurs (1953) selected 18 patients from their psychiatric clinic in Toronto, 10 of whom had clinical epilepsy and eight of whom suffered from episodic psychiatric manifestations, with electroencephalographic abnormalities in the temporal lobes, but no true seizures. "Mysoline" produced a significant reduction of fits in nine of their 10 epileptic patients, but had no effect on the eight psychiatric patients. They found favourable personality changes in five of their patients, and remark on the absence of serious toxic effects, though one of their patients developed a rash apparently due to the drug.

Butter (1953) reported his observations on 53 sane male epileptics at the Saint David's Hospital, Edmonton, England. All his patients had proved resistant to other anti-convulsants in full dosage, and the period of his trial extended over fifteen months. The frequency of fits was

reduced by 25% or more in 35% of his cases, and in a further 15% the patients "felt better", though there was no significant reduction in their fit incidence. Treatment was discontinued in 50% of his series, either because the patients felt drowsy or because the number of their seizures had not decreased. Apart from drowsiness he found no disagreeable side-effects or toxic changes.

Adderley and Monro (1953) found the drug an efficient anti-convulsant in epileptics with associated mental disorder, and remark on the dramatic improvement in behaviour and sociability of some of their patients, though the more psychotic subjects did not show this favourable response.

Calnan and Borrelli (1953) describe abolition of fits in four of six patients with major epilepsy treated with "Mysoline" for nine months, and comment that two of their patients felt much better and more energetic during "Mysoline" therapy than when receiving other drugs.

#### The Present Investigation.

This clinical trial was begun in November, 1952. The patients were selected from out-patients attending the R.S.L. Northcott Neurological Centre and the out-patient department of the Royal Prince Alfred Hospital. The sole criterion for their selection was that their fits had proved resistant to other anti-convulsants in full dosage and in various combinations over a period of at least six months, though in the majority of cases this period extended to several years. At the time of starting the trial their condition was the best that could be achieved with the other anti-convulsants.

Accurate information regarding the fit incidence during the six months preceding the trial was available in almost all cases, either from our case records or from the patients and their relatives, many of whom had kept a diary of their seizures. The patients were told of the change in their treatment and were asked to keep accurate details of their seizures and to report for review at monthly intervals. It was realized that this might introduce an error in the assessment of the results, for epileptics frequently show temporary improvement when starting on any new form of therapy. However, there appeared to be no certain method of avoiding this difficulty. Handley and Stewart had given inert tablets indistinguishable from "Mysoline" to a control group at the beginning of their trial, but dropped this method after two months, because the difference in response of the treated and control groups was so great as to leave no doubt that the drug was responsible.

Whereas in the clinical trials so far reported "Mysoline" was used alone in the majority of cases, I decided to determine its efficiency in combination with other anti-convulsants. This decision was based on previous experience that with most epileptics better results can be achieved with a combination of drugs than with one single compound. Also the toxic reactions and side-effects of the individual drug can often be avoided by using each drug in relatively smaller dosage. Two patients, however, were not taking any anti-convulsants at the time when "Mysoline" therapy was begun, and both responded well to this drug alone.

Of the 30 patients intended for the trial, six had to be dropped or excluded from the analysis of results: one has been receiving the drug for four months only though free from fits; one failed to return for review after the first month of treatment; one was found to harbour a cerebral tumour a few weeks after starting "Mysoline" therapy, though the results of earlier complete neurosurgical investigations had proved negative; two admitted to having been most irregular in taking their tablets, and one of these was found to have hysterical fits in addition to her epileptic seizures; the sixth was suffering from juvenile *petit mal* (pyknolepsy), and "Mysoline" therapy was abandoned after four weeks during which the patient showed no improvement.

This leaves 24 patients, nine of whom have taken the drug for eight months, five for seven months and 10 for six months. Because of this variation in the period of

<sup>1</sup> "Mysoline" is the registered trade-mark of Imperial Chemical (Pharmaceuticals) Limited.

treatment, it was thought preferable to state the results in terms of monthly average fit incidence rather than as the total number of seizures during the trial period. Neither method, however, could give a complete indication of the distribution of seizures. One patient, for example, who had averaged 16 major fits a month during the six months preceding the trial, had 10 milder *grand mal* seizures on one day while receiving "Mysoline" and no more during the remainder of her six months' treatment with this drug.

Twelve of the patients were males and 12 were females. Their ages ranged from five years to fifty-one years, and five of them were children under fourteen years of age.

The history of the duration of epilepsy varied from six months to thirty-nine years. Eighteen of the patients, or 75%, had taken fits for more than five years.

#### Clinical Types of Epilepsy.

With regard to clinical types of epilepsy, 17 cases were diagnosed as "idiopathic" epilepsy; in these no family history was known, and no other cerebral abnormality was found on investigation. Two cases came into the category of genetic epilepsy, but in one of these the patient was found to have generalized cerebral atrophy on air encephalography. Four patients suffered from epilepsy secondary to cerebral damage from birth injury or unknown causes, and three of these were mentally deficient. One patient had epilepsy associated with microcephaly.

TABLE I.  
Types of Seizures.

Type of Seizure.	Number of Cases.
Major fits only .. .. .	1
Minor motor seizures only .. .. .	1
Psycho-motor attacks only .. .. .	1
Major fits and minor motor seizures ..	16
Major fits and psycho-motor attacks ..	4
Major, minor motor and psycho-motor seizures .. .. .	1

The electroencephalogram was abnormal in all 24 cases and, in general, was consistent with the clinical diagnosis.

#### Types of Seizures.

The following are the types of seizures referred to. (i) The term "major fit" ("M" in the table) is used only for true *grand mal* attacks and implies loss of consciousness, rigidity and convulsions. (ii) "Minor motor" seizures ("m-m" in the table) are physiologically related to *grand mal* and not to true *petit mal*. They are suppressed or "larval" major fits with impairment or loss of consciousness for from a few seconds to two minutes. Though the patient may fall, there is little rigidity and no convulsions. In this group are also included auras which do not develop into a fit, and the momentary absences so common in the majority of epileptics. (iii) The term "psycho-motor" attack ("p-m" in the table) is used in the definition of Gibbs (1947)—"periods of confusion with inco-ordination and apparently purposeful movements". In our series it includes also the temporal lobe seizures consisting of a transient sensation of unwarranted and intense familiarity with a new experience, the *déjà vu* phenomenon, or of momentary hallucinations of taste or smell.

Table I shows the distribution of the types of seizure in the 24 cases under review. Twenty-two patients had suffered major convulsions during the six months prior to starting on "Mysoline" therapy, while the remaining two patients had taken major fits earlier in their epileptic career, but had none during the six months preceding the trial.

#### Dosage.

At the beginning of the trial "Mysoline" was introduced fairly rapidly; treatment began with one tablet of 0.25

gramme twice daily, and a further tablet was added at intervals of three days. Side-effects of drowsiness and ataxia were rather distressing with this method, and it was decided to introduce the drug more slowly. As most of the patients had suffered from epilepsy for several years there appeared to be no cause for hurry, and the following dosage scheme was adopted (Table II):

TABLE II.

Stage of Treatment.	Number of Tablets Given.		
	Morning.	Noon.	Evening.
First week .. .. .	—	—	1
Second week .. .. .	1 <sup>1</sup> / <sub>2</sub>	1 <sup>1</sup> / <sub>2</sub>	1
Third week .. .. .	1	1	1
Fourth week .. .. .	1	1	1

Patients who were taking phenobarbitone or "Prominal" before starting on "Mysoline" were asked to omit the evening dose during the third week, the noon dose during the fourth week and the morning dose in the fifth week.

If side-effects were not great, or if fits persisted, a fourth tablet was then given with the evening dose, and in seven cases two further tablets were added at weekly intervals. It was found that two tablets three times daily, or 1.50 grammes per day, was the most patients would tolerate without distressing side-effects. Nine of the 19 adult patients could not tolerate more than four tablets, or 1.00 gramme, per day and complained of severe drowsiness or ataxia if the dose was increased beyond this.

The distribution of tablets must also be determined in accordance with the time incidence of fits, and patients with predominantly nocturnal seizures were found to respond best to one tablet in the morning, one at mid-day and two at night.

As "Mysoline" is chemically related to phenobarbitone and thus belongs to the sedative group of anti-convulsants, which are thought to protect the unstable brain from the epileptic discharge, 22 of the patients in this series were asked to continue taking hydantoins, "Dilantin" or "Mesantoin", which are said to act by inhibiting the epileptic process directly without depressing cerebral activity.

The final dose of "Mysoline" varied with each individual patient, and was usually the maximum amount that the patient would tolerate without complaining of any persistent unpleasant side-reactions.

The dose of "Mysoline" taken by the 19 adult patients is shown in Table III.

TABLE III.  
Dosage of "Mysoline" Used.

Daily Dose of "Mysoline" (Grammes) in Divided Doses.	Number of Cases.
0.75	4
0.88	1
1.00	4
1.25	3
1.50	7

The dose used for the five children varied with their ages, and all of them tolerated the drug well.

As the drug was introduced slowly in all but three cases of this series, the "period of 'Mysoline' therapy" for the purpose of analysis of the results was calculated from the first day when a daily dose of 0.75 gramme of "Mysoline" was taken, excepting in one case (that of a child) in which a final dose of 0.37 gramme a day was established.

TABLE IV.  
Summary of Clinical Details and Response to "Mysoline" Therapy of Twenty-four Patients.

Patient, Sex, Age.	Clinical Diagnosis.	Electro- encephalogram.	Dura- tion Epi- lepsy, (Years).	Previous Therapy.	Monthly Average Fit Incidence During Six Months Before "Mysoline".			Period of "My- soline" Therapy (Months).	Daily Dose of "My- soline" (Grammes).	Drugs Given with "Mysoline".	Monthly Average Fit Incidence on "Mysoline" Therapy.			Side-Effects.	Percentage Reduction of Fits.		
					M.	m-m.	p-m.				M.	m-m.	p-m.		M.	m-m.	p-m.
S.C. F. 8	Epilepsy and mental deficiency secondary to brain damage. AEG: normal.	Basic 4-5 c.p.s. with numerous atypical wave and spike complexes.	6.5	"Dilantin" and phenobarbitone in large doses.	>70	Occasional.	—	8	1.25	"Dilantin."	11	2	—	Drowsiness and ataxia for first four weeks.	84	?	—
J.F. F. 19	"Idiopathic" epilepsy, grand mal. AEG: normal.	8 c.p.s. alpha with random bilateral 5-7 c.p.s. activity.	16	"Dilantin", "Mesantoin", phenobarbitone, "Prominal".	13	Num- erous.	—	8	1.50	"Dilantin" and "Prominal".	4	2	—	Drowsiness, ataxia, anorexia, nausea, blurring of vision for four weeks.	69	?	—
B.K. F. 28	"Idiopathic" epilepsy, grand mal and psychomotor.	Bilateral 5-7 c.p.s. paroxysms of high voltage.	6	"Dilantin", "Prominal", phenobarbitone, "Tridione".	2	—	>90	8	1.25	"Dilantin."	None.	—	>40	Slight drowsiness for first six weeks.	100	—	33
D.M. M. 37	"Idiopathic" epilepsy, grand mal.	8-9 c.p.s. rhythm with occasional bilateral 5-7 c.p.s. paroxysms.	9	"Dilantin" phenobarbitone.	3	>450	—	8	1.50	None.	None.	5	—	Slight drowsiness and giddiness for first two weeks.	100	87	—
C.S. F. 34	"Idiopathic" epilepsy, grand mal.	Paroxysms of 3 c.p.s. wave and spike discharges.	16	"Dilantin", phenobarbitone, bromide.	3	Occasional.	—	8	1.00	"Dilantin."	0.13	Rare.	—	Drowsiness, ataxia and giddiness for first three weeks.	96	?	—
R.T. M. 22	Genetic epilepsy, grand mal and psychomotor. AEG: general cortical atrophy.	Bilateral 5-7 c.p.s. waves, and 4-7 c.p.s. activity with spikes in right temporal region.	10	"Dilantin", "Mesantoin", phenobarbitone, "Prominal".	5	—	2	8	1.00	"Dilantin" and "Mesantoin".	4	—	1	Severe drowsiness, ataxia, blurring of vision for four weeks.	20	—	50
P.A. M. 21	"Idiopathic" epilepsy, grand mal and psychomotor.	9-10 c.p.s. alpha with bilateral 4-7 c.p.s. waves.	13	"Dilantin", phenobarbitone, "Prominal".	1	—	2	8	1.50	"Dilantin" and "Mesantoin".	None.	—	1	None.	100	—	50
L.C. M. 26	"Idiopathic" epilepsy, grand mal.	Diffuse slow wave changes with bilateral 4-7 c.p.s. waves.	11	"Dilantin", "Mesantoin", "Prominal".	1	0.5	—	8	1.50	"Dilantin."	0.13	0.13	—	Drowsiness for four weeks; ataxia and giddiness for two weeks.	87	75	—
R.R. F. 12	Epilepsy and mental deficiency due to brain damage from birth injury.	Basic 7 c.p.s. rhythm with paroxysms of 4-7 c.p.s. waves and 3-5 c.p.s. activity in left temporal region.	6.5	"Dilantin", phenobarbitone, "Tridione", "Paraldehyde".	—	>200	—	8	1.00	"Dilantin" and "Tridione".	—	None.	—	Drowsiness and ataxia for four weeks.	—	100	—
J.F. M. 5	"Idiopathic" epilepsy, grand mal. Angiograms: normal.	Basic 5-6 c.p.s. rhythm with high voltage bilateral 3 c.p.s. waves.	0.5	"Dilantin", phenobarbitone.	8	Num- erous.	—	7	0.75	"Dilantin" and phenobarbitone.	None.	None.	—	Anorexia and slight dizziness for first few days.	100	100	—
M.C. F. 31	"Idiopathic" epilepsy, grand mal.	Basic 4-7 c.p.s. rhythm with bilateral paroxysms of atypical wave and spike.	28	"Dilantin", phenobarbitone, "Prominal", "Tridione".	12	Occasional.	—	7	1.50	"Dilantin."	None.	Occasional.	—	Drowsiness and slight ataxia for first two months.	100	?	—

M. = major fit; m-m. = minor motor seizure; p-m. = psycho-motor attack; AEG = air encephalogram.

TABLE IV.—Continued.  
Summary of Clinical Details and Responses to "Mysoline" Therapy of Twenty-four Patients.—Continued.

Patient, Sex, Age.	Clinical Diagnosis.	Electro- encephalogram.	Duration of Epi- lepsy. (Years.)	Previous Therapy.	Monthly Average Fit Incidence During Six Months Before "Mysoline".			Period of "My- soline" Therapy. (Months.)	Daily Dose of "My- soline". (Grammes.)	Drugs Given with "Mysoline".	Monthly Average Fit Incidence on "Mysoline" Therapy.			Side-Effects.	Percentage Reduction of Fits.		
					M.	m-m.	p-m.				M.	m-m.	p-m.		M.	m-m.	p-m.
J.T. M. 26.	"Idiopathic" epilepsy, <i>grand mal</i> and psycho- neurosis.	Slow wave dys- rhythmia with 3 c.p.s. wave and spike discharges.	9	"Dilantin", pheno- barbitone, "Pro- minal".	10	Occa- sional.	—	7	1.00	"Dilantin" and "Prominal".	8	5	—	Drowsiness, ataxia, anorexia, blurring of vision for five weeks.	20	Worse.	—
B.R. M. 13.	"Idiopathic" epilepsy, <i>grand mal</i> , and right focal seizures.	Basic 5-6 c.p.s. high voltage rhythm with oc- casional 3-5 c.p.s. waves.	5	"Dilantin", "Me- santoin", "Pro- minal", pheno- barbitone, "Tri- dione".	1	20	—	7	0.75	"Mesantoin" and "Tridione".	0.3	5	—	Slight drowl- iness and ataxia for first few days.	70	75	—
G.M.C. M. 16.	Epilepsy and right spastic paralysis due to birth trauma. AEG: normal.	Basic 4-7 c.p.s. rhythm of varying amplitude.	6	"Dilantin", pheno- barbitone, "Pro- minal".	2	Occa- sional.	—	7	0.88	"Dilantin."	0.7	Rare.	—	Drowsiness, ataxia and giddi- ness for first two weeks.	66	?	—
P.S. F. 23.	"Idiopathic" epilepsy, <i>grand mal</i> . Angiograms: normal.	Irregular 9-10 c.p.s. rhythm with bilateral paroxysms of 5-7 c.p.s. waves.	5	"Dilantin", pheno- barbitone, "Pro- minal".	1	Occa- sional.	—	6	0.75	"Dilantin."	None.	0.5	—	Drowsiness for first three weeks.	100	?	—
J.O'B. F. 24.	"Idiopathic" epilepsy, <i>grand mal</i> .	Irregular basic rhythm with bi- lateral 5-7 c.p.s. paroxysms.	21	"Dilantin", pheno- barbitone.	16	Occa- sional.	—	6	1.50	"Dilantin."	1.6	Rare.	—	Slight drowl- iness, dizziness, anorexia for first four weeks.	90	?	—
J.R. F. 17.	"Idiopathic" epilepsy, <i>grand mal</i> .	9-10 c.p.s. alpha with bilateral 5-7 c.p.s. waves.	6	"Dilantin", pheno- barbitone, "Pro- minal".	1	25	—	6	1.25	"Dilantin."	0.3	1.5	—	Drowsiness and ataxia for two days.	70	94	—
K.A. M. 40.	Epilepsy, mental deficiency and left hemiplegia due to birth trauma.	Bilateral 6-8 c.p.s. activity with 3-6 c.p.s. waves over right temporal region.	39	"Dilantin", pheno- barbitone, "Pro- minal".	10	—	—	6	1.00	"Dilantin".	None.	—	—	Occasional drowl- iness and ataxia in first four weeks.	100	—	—
W.K. M. 28.	"Idiopathic" epilepsy, psychomotor seizures.	9-10 c.p.s. alpha with few scattered 5-7 c.p.s. waves on overbreathing.	3	None.	—	—	10	6	0.75	None.	—	—	0.3	Severe ataxia and nausea on first day only. Slight drowl- iness for three weeks.	—	—	97
T.H. F. 16.	Major epilepsy with micro- cephaly.	5-7 c.p.s. dominant rhythm with paroxysmal ac- tivity.	14	"Dilantin", pheno- barbitone, "Pro- minal".	2	Occa- sional.	—	6	1.25	"Dilantin."	0.15	0.6	—	Drowsiness and occasional giddi- ness for first two weeks.	92	?	—
E.S. M. 32.	"Idiopathic" epilepsy, <i>grand mal</i> . AEG: normal.	9-10 c.p.s. alpha with bilateral 5-7 c.p.s. waves on overbreathing.	1.5	"Dilantin."	1	1	—	6	0.75	"Dilantin."	None.	None.	—	Drowsiness for three months. Blurring of vision for two weeks.	100	100	—
V.G. F. 19.	Genetic epilepsy, <i>grand mal</i> and psycho-motor.	9-10 c.p.s. alpha with bilateral paroxysms of 6-8 c.p.s. waves.	3	"Dilantin", pheno- barbitone.	1	Occa- sional.	10	6	0.75	"Dilantin" and "Prominal".	1	3	10	Drowsiness for first two weeks.	0	Worse.	0

M. = major fit; m-m. = minor motor seizure; p-m. = psycho-motor attack; AEG = air encephalogram.

TABLE IV.—Continued.  
Summary of Clinical Details and Response to "Mysoline" Therapy of Twenty-four Patients.—Continued.

Patient, Sex, Age.	Clinical Diagnosis.	Electro- encephalogram.	Dura- tion of Epi- lepsy. (Years.)	Previous Therapy.	Monthly Average Fit Incidence During Six Months Before "Mysoline".			Period of "My- soline" Therapy. (Months.)	Daily Dose of "My- soline". (Grammes.)	Drugs Given with "Mysoline".	Monthly Average Fit Incidence "Mysoline" Therapy.			Side-Effects.			Percentage Reduction of Fits.		
					M.	m-n.	p-m.				M.	m-n.	p-m.				M.	m-n.	p-m.
A.C. M. 51.	"Idiopathic" epilepsy of late onset. AEG: normal. Angiograms: normal.	Low voltage basic rhythm; oc- casional 5-7 c.p.s. waves in left temporal region.	4	"Dilantin", pheno- barbitone.	1.5	—	1	6	1.50	"Dilantin."	None.	—	2	Slight drowsi- ness and giddi- ness for first few days.	100	—	100	—	Worse.
F.F. F. 7.	"Idiopathic" epilepsy, <i>grand mal</i> .	High voltage 8-9 c.p.s. rhythm with paroxysms of bi- lateral 4-7 c.p.s. activity.	4	"Dilantin", pheno- barbitone.	0.8	Rare.	—	6	0.37	"Dilantin."	None.	0.2	—	Slight drowsi- ness for first few days.	100	?	100	?	—

M. = major fit; m-n. = minor motor seizure; p-m. = psycho-motor attack; AEG = air encephalogram.

#### Results of Treatment.

The manifestations of epilepsy are so complex, capricious and variable that no absolutely rigid criteria are possible in assessing the value of a new drug. Two factors from which we can determine our results are (i) reduction in the number of attacks, which can be established with reasonable accuracy, and (ii) changes in the quality of attacks, or in the patient's general feeling of well-being, which are essentially subjective and therefore influenced by psychological factors, such as the patient's hope of cure from the new drug, or his fear of being a "guinea-pig" in a medical experiment.

Although 13 patients who continued having seizures while receiving "Mysoline" reported that these were milder than their fits before taking the drug, no account was taken of this in the statistical analysis of the results of treatment, which is based solely on the reduction in the number of attacks.

Table IV gives the clinical details, the drugs used and their dosage, and the fit incidence before and during "Mysoline" therapy for each of the 24 patients.

The results of treatment for the entire series are summarized in Table V. Improvement is regarded as significant if the number of seizures decreased by two-thirds or more during the period of "Mysoline" therapy as compared with the preceding six months.

Table VI analyses the effect of "Mysoline" therapy on the individual types of seizures. Although 18 patients suffered from minor motor seizures, the effect of the drug on this type of attack could be assessed only in nine, as the others were unable to provide reliable data of the frequency of these seizures either before or during "Mysoline" treatment.

Patients who had both major fits and minor motor seizures were regarded as improved if the number of major fits decreased by two-thirds or more, and if—though uncertain of the exact number—they considered the incidence of minor attacks no greater than before starting on "Mysoline" therapy.

The psycho-motor type of attack showed the least response to treatment, only one of six patients being significantly improved. Of the five other patients in this group two reported a 50% reduction, and one a 33% reduction in the number of their seizures; in one case their frequency remained unchanged, and the fifth patient paid for the abolition of his major fits with an increase in the number of psycho-motor attacks.

In two of the three cases in which major fits failed to improve, the minor motor seizures did likewise, while in the third the incidence of psycho-motor attacks was reduced by one-half.

Three of the 10 patients who remained free from major fits after starting on "Mysoline" therapy had averaged from eight to 12 seizures a month prior to taking the drug. One child who has remained free from all attacks during eight months on "Mysoline" therapy previously used to suffer from more than 200 minor motor seizures each month, in spite of large doses of a variety of anti-convulsants.

These figures, however, cannot give us the complete picture of the improvement reported by some of the patients, 10 of whom spontaneously remarked on a feeling of well-being that they had missed for years, or mentioned an increase in mental alertness and in their capacity for work. Three patients who had been dependent on an invalid pension because their fits precluded employment were able to return to work, and the parents of four of the five children described a considerable improvement in their behaviour.

#### Side-effects.

Only one of the 24 patients experienced no side-effects at all. The other 23 complained mostly of drowsiness and of difficulty in getting out of bed in the morning, and 18 of them experienced giddiness, a feeling of drunkenness and some ataxia. These symptoms were only mild in 11 cases and moderately severe in 12; in some of the latter they

prevented an increase in dosage. An analysis of the incidence of side-effects is shown in Table VII.

In all 23 patients the side-effects passed off after periods varying from one day to three months, in spite of continuation of treatment, but several patients complained of renewed drowsiness and giddiness lasting a few days each time the dose was increased. One man experienced severe ataxia and nausea after the first two tablets, but none afterwards. The variation in the duration of side-effects is shown in Table VIII.

The emotional disturbances observed in six cases merit some further discussion. Three patients developed hysterical manifestations while under treatment with "Mysoline". Two of them presented with hysterical fits

TABLE V.  
Results of Treatment.

Result.	Number of Patients.
Free from attacks . . . . .	4 (16.6%)
Reduction of two-thirds or more . .	16 (66.8%)
No significant improvement . . . . .	4 (16.6%)

which I was fortunate enough to witness, while the third exhibited a severe hysterical ataxia, paresis of the legs and blindness, all of which disappeared after the patient had spent three days in hospital without interruption of "Mysoline" therapy. Two of these patients had been under psychiatric care for several years, and all three recovered from their functional symptoms though "Mysoline" therapy was continued.

One young woman complained of emotional lability and presented with attacks of unprovoked and uncontrollable weeping, which ceased after the first four weeks on "Mysoline" therapy. Two patients mentioned transient unpleasant feelings of tension and had brief temper out-

TABLE VI.  
Analysis of Results of Treatment in the Different Types of Seizure.

Type of Seizure.	Number of Patients.	Free from Attacks.	Improved.	Not Improved.
Major fits . . . . .	22	10 (45.5%)	9 (40.9%)	3 (13.6%)
Major fits and minor motor seizures . . . . .	17	2 (11.8%)	13 (76.4%)	2 (11.8%)
Minor motor seizures . . . . .	9	3 (33.3%)	4 (44.4%)	2 (22.3%)
Psycho-motor attacks . . . . .	6	—	1 (16.6%)	5 (83.4%)

bursts, which appeared to replace their fits; these were completely controlled by "Mysoline". Both patients, however, preferred these unpleasant sensations to their fits and chose to continue with the treatment.

Finally, when the frequency of side-effects of a new drug is assessed, it must be appreciated that the specific inquiry for these symptoms in a clinical trial may induce the patient to take note of minor discomforts which he would ordinarily have disregarded.

#### Discussion.

The accurate evaluation of a new drug for the treatment of epilepsy is difficult because of a number of problems. When the trial is carried out with out-patients one has to depend entirely on the history obtained from them, while even in an epileptic colony or hospital some of the patients' seizures may remain unobserved. There are no physical signs in this disease by which we can watch the patient's progress, and no laboratory tests to compare with our clinical impressions.

Unfortunately, the reduction or abolition of seizures is not always accompanied by a change in the patient's electroencephalogram, and no reliable conclusions can be drawn from this method of investigation.

The use of a control group of patients, as was pointed out earlier, is beset with many difficulties, and so one is left with only the patient as his own control.

The regular contact with the patients in a clinical trial enables the physician to assess the reliability of their histories with reasonable confidence. Most of the patients in this series cooperated willingly and conscientiously and kept accurate records of their attacks. Only two patients were found to have been irregular in taking the drug and were dropped from the trial, and in only one of the cases included in the trial was some doubt left as to the regularity of the dosage.

TABLE VII.  
Incidence of Side Effects.

Symptom.	Number of Patients.
Drowsiness . . . . .	22
Giddiness . . . . .	18
Ataxia . . . . .	13
Slurring of speech . . . . .	1
Difficulty with visual accommodation . .	4
Anorexia . . . . .	4
Nausea . . . . .	2
Emotional disturbances . . . . .	6

No skin rashes were observed. Regular blood counts were available in only eight cases and showed no abnormality, and no albumin was found on repeated examination of the urine in 16 cases.

Epilepsy is a chronic disease, and the incidence of fits in any one patient may vary widely from month to month. Most of the patients in this trial, however, took fits sufficiently often to permit us to draw reasonable conclusions from a period of observation over six to eight months. As the number of patients in this trial was

TABLE VIII.  
Duration of Side-Effects.

Duration of Side-Effects.	Number of Cases.
Less than one week . . . . .	5
One to four weeks . . . . .	14
Four to eight weeks . . . . .	3
Twelve weeks . . . . .	1

relatively small, it was decided to choose the rigid criterion of a reduction in the fit incidence of two-thirds or more before considering the patient improved.

All but one of the 22 patients who were given other anti-convulsants with "Mysoline" had been taking the same drugs in equal or larger doses before the trial. Any reduction in the number of their seizures must, therefore, be due to "Mysoline" therapy.

The result of this trial, showing significant improvement in 20 out of 24 patients (83.4%) suffering from major fits, can leave no doubt that "Mysoline" is an efficient drug in the treatment of *grand mal* epilepsy. Its efficiency in the control of psycho-motor seizures was, however, not nearly as encouraging, and it failed in the one case of juvenile *petit mal* in which it was used. Studies of larger series of patients suffering from the latter two varieties of attacks will be necessary before arriving at a definite conclusion.

The absence of any serious toxic effects, reported in the literature to date and confirmed in this trial, is most encouraging and indicates that "Mysoline" may be used safely for out-patients without laboratory control.

The disappearance of side-effects after the first few weeks of treatment in almost all cases further adds to the value of the drug, and it may be predicted with some confidence that "Mysoline" will prove to be one of the most useful anti-convulsants at our disposal.

### Summary.

1. In 24 refractory cases of epilepsy the patients were treated with "Mysoline" for periods from six to eight months; in 22 of these the drug was used in combination with another anti-convulsant.

2. Four patients (16.6%) remained free from all attacks, and a further 16 (66.8%) reported a reduction in the number of their seizures by two-thirds or more.

3. *Grand mal* fits were significantly reduced in 19 of 22 cases, but only one of six patients suffering from psychomotor attacks showed a favourable response.

4. The drug should be introduced gradually to the maximum each patient can tolerate without experiencing side-effects. A dose of 1.5 grammes daily was found to be well tolerated by most patients.

5. Side-effects include drowsiness, dizziness, ataxia and disturbances of visual accommodation, but almost invariably pass off after the first few weeks of treatment.

6. No serious toxic effects were encountered.

7. The results of this trial are discussed, and it is felt that "Mysoline" is a valuable drug in the treatment of *grand mal* epilepsy.

### Acknowledgements.

I am indebted to Imperial Chemical Industries of Australia and New Zealand, Limited, for a generous supply of "Mysoline".

I wish to thank Dr. L. Rail for the electroencephalographic reports on the patients discussed in the trial.

My thanks are also due to all the patients, who have cooperated willingly and conscientiously.

### References.

- ADDERLEY, D. J., and MONRO, A. B. (1953), "Mysoline in the Treatment of Epilepsy", *Lancet*, 1: 1154.
- BOGUE, J. Y., and CARRINGTON, H. C. (1953), "The Evaluation of 'Mysoline'—A New Anticonvulsant Drug", *Brit. J. Pharmacol.*, 8: 230.
- BONKALO, A., and ARTHURS, R. G. S. (1953), "Mysoline in the Treatment of Epileptic and Non-Epileptic Psychiatric Patients", *Canad. M. A. J.*, 68: 570.
- BUTTER, A. J. M. (1953), "Mysoline in the Treatment of Epilepsy", *Lancet*, 1: 1024.
- CALNAN, W. L., and BORRELLI, V. M. (1953), "Mysoline in the Treatment of Epilepsy", *Lancet*, 2: 42.
- GIBBS, F. A. (1947), "New Drugs of Value in the Treatment of Epilepsy", *Ann. Int. Med.*, 27: 548.
- HANDLEY, R., and STEWART, A. S. R. (1952), "Mysoline: A New Drug in the Treatment of Epilepsy", *Lancet*, 1: 742.
- SELBY, G. (1953), "The Drug Treatment of Epilepsy", *M. J. AUSTRALIA*, 1: 471.
- SMITH, B. H., and MCNAUGHTON, F. L. (1953), "Mysoline, A New Anti-convulsant Drug. Its Value in Refractory Cases of Epilepsy", *Canad. M. A. J.*, 68: 464.

### SURGICAL TREATMENT OF RECURRENT PAROTITIS.

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INFLAMMATION of the parotid salivary gland is most commonly seen in epidemic form due to the specific infection of mumps. Far less common is suppurative parotitis, which develops in debilitated patients as a post-operative complication or during the course of a severe illness. There is, however, a third variety of parotitis, which is far from rare, and which, because of its tendency to recurrence, may cause a significant degree of disability. Described as recurrent or chronic parotitis, it occurs more frequently in children than in adults, but may be seen at any age. Treatment of the condition is unsatisfactory, and the commonly used measures are not very effective in preventing

recurrences, although some amelioration of the attack itself may be obtained. This has led us to perform total parotidectomy for this condition, and two cases are reported below. The technique of the operation is such that integrity of the facial nerve is ensured.

### Clinical Features.

An excellent account of the condition has been given by Bigler (1946), who described the findings in 60 cases. In 12 cases which have come to our notice we have seen no significant variation from the description as presented by him, although more of our patients have been adults.

The onset of the attack is marked by discomfort, soon followed by swelling in one parotid salivary gland. In approximately two-thirds of the cases the disease remains on the same side in the first and in any subsequent attack.



FIGURE 1.

Mrs. A.R., one year after operation, showing good contraction of the facial muscles and hence integrity of the nerve.

In the remaining third the other parotid gland becomes involved later in the first attack or in one of the recurrences, and in some cases the parotid glands are affected alternately in succeeding attacks. The swelling may remain for a few hours only, more commonly it lasts for several days, and in some it persists for two or three weeks. Mastication may have little effect on the size of the swelling but usually increases the discomfort.

During the attack the opening of Stensen's duct is reddened. Pressure over the duct may produce turbid saliva, but in the first twenty-four hours the opening appears dry and no fluid is obtained even on cannulization of the duct.

Fever may occur, but in many cases it is of mild degree only, and there is often little constitutional disturbance, particularly in older children and adults. Culture of the fluid from the duct yields a growth of *Streptococcus viridans* in almost all cases, but the pneumococcus and *Staphylococcus aureus* are occasionally present.

X-ray examination of the gland and duct rarely demonstrates a calculus. X-ray examination after injection of lipiodol into Stensen's duct may show dilatation of the ducts within the gland, but this is not common. In most cases the duct system is within normal limits and there is no demonstrable sialoangiectasis.

The parotid gland swelling usually subsides completely at the end of the attack, but in cases with a long history of recurrences there is persistent swelling of some degree and the gland feels firmer than normal. Possibly there are cases of non-specific parotitis in which only one attack occurs and such cases present no problems in treatment. However, the disease is distinguished by its tendency to recur at intervals varying from weeks to months or even years. In many cases the attacks tend to become less frequent and less severe over a period of years, but in others the frequency and severity remain unaltered or increase.

Many measures have been used in the treatment of this condition. The early attacks appear to respond to symptomatic treatment, and of recent years penicillin has often been given the credit for subsidence of the swelling after

#### Reports of Cases.

CASE I.—Mrs. A.R., aged twenty-eight years, was examined by one of us (G.M.) on November 30, 1951. She complained of recurrent swelling of the right side of her face of ten years' duration. The attacks had become increasingly frequent and severe in the preceding two years, the swelling remaining for two or three weeks at a time. In the previous month the gland had been constantly swollen, with exacerbation of swelling and discomfort when she attempted to eat. This, together with frequent discharge of purulent saliva into her mouth from time to time, had prevented her from eating solid food. She had been unable to work during recent attacks and was considering resigning from her position. During the ten-year period she had had X-ray examination of the parotid region on several occasions, including a lipiodol injection six months before. This had shown no abnormality of the gland. Treatment had included regular massage of the gland and duct dilatation, as well



FIGURE II.

Photograph of Mrs. A.R., one year after operation, showing the good cosmetic result.

#### Treatment.

a few days. Continuing attacks lead to investigation by X rays, perhaps followed by dilatations of the duct orifice with or without instillation of antiseptics or antibiotics. Septic foci are sometimes regarded as a cause of the attacks and tonsillectomy and dental extractions follow. X-ray therapy to the parotid gland has been used, and it is stated that after radiation therapy the attacks become less frequent and severe. Bigler reported on its use in a number of cases in his series, and noted that there was some but variable improvement in these patients.

All these methods of treatment have been stated to produce improvement and in some cases a complete cessation of attacks. But there are undoubtedly many cases in which the use of all these procedures in turn does not prevent recurrence. This has led to surgical intervention aimed at denervating the affected gland by avulsion of the auriculo-temporal nerve. Only two cases in which this has been done have come to our notice, but both patients have continued to experience attacks of the disease.

In severe cases in which repeated attacks occur at short intervals, it is often found that all these methods of treatment are unsatisfactory. Two such cases are reported here, and it is suggested that the treatment used—total parotidectomy—is indicated for patients with a similar degree of disability from this disease.



FIGURE III.

Photograph of B.T., two months after operation, showing contraction of the facial muscles. There is still some slight lower facial weakness.

as the systemic administration of penicillin and symptomatic measures during exacerbations. There had never been any swelling of the other parotid gland.

Examination of the patient revealed a firm, slightly tender enlargement of the right parotid gland. The opening of Stensen's duct was reddened, and pressure over the gland produced turbid saliva from the duct orifice. Culture from this subsequently yielded a growth of *Streptococcus viridans*. Another X-ray examination revealed a small opacity in the region of the duct orifice, and although no calculus could be felt it was thought advisable to explore the duct. This was done under local anaesthesia on December 17, but no calculus was found. A probe passed readily into the duct, with no suggestion of obstruction by stricture.

On January 2, 1952, she reported that the swelling had been more painful in the preceding ten days. Instillation of penicillin into the duct combined with massage and the local application of heat to the gland had produced no improvement. She had not been able to work during this time.

On February 21, 1952, total parotidectomy was carried out. Her post-operative course was uneventful and at no stage was there any sign of facial weakness. She was discharged from hospital after eight days. Examination of sections of the parotid gland revealed dilatation of the larger tributaries of the duct system, perilobular fibrosis and replacement of the parenchyma by fat, with some foci of round-cell infiltration.

She was last examined on March 31, 1953, when the accompanying photographs were taken (Figures I and II). She had had no further symptoms. The scar and the depression behind the mandible due to absence of the parotid gland are not conspicuous, and she considers them a small price to pay for relief from her disability.

CASE II.—B.T., a boy, aged ten and a half years, was referred to one of us (H.H.E.) by Dr. J. Long, of Bendigo, on December 9, 1952. The child's mother stated that the right parotid gland had first become enlarged two years previously, and the swelling had recurred at frequent intervals, each episode lasting two or three weeks. During the last six months the swelling of the gland had not subsided completely between attacks. In each attack the gland was painful and the child felt ill, so much so that he had spent more time at home than at school over the last two years. Eating did not increase the size of the gland but made the swelling more painful. Treatment had been ineffective;



FIGURE IV.  
Photograph of B.T., two months after operation,  
showing the good cosmetic result.

sulphonamides, penicillin injections and irrigation of the duct with a variety of antiseptic solutions had all failed to prevent recurrence. X-ray examination of the gland area did not reveal a calculus.

Because of the incapacitating nature of the condition and the lack of response to conservative treatment, total parotidectomy was advised, and this was performed on January 7. The post-operative course was uneventful, and the child was discharged from hospital five days later. For about one month after operation there was some lower facial weakness; this had almost completely recovered when the boy was examined on March 13 and his photographs were taken (Figures III and IV). The scar of operation is not very obvious and the parents are well pleased with the result.

#### Total Parotidectomy for Recurrent Parotitis.

It is not suggested that total parotidectomy is often required in the treatment of this condition. Most patients progress through a varying number of recurrences to a state of freedom from attacks, and this may be hastened by the conservative measures commonly used in treatment. But cases do occur in which the disease becomes more severe as attack succeeds attack and more radical treatment is demanded. There is rarely any hesitation in advising the excision of a submandibular salivary gland which has become the site of chronic infection, with or without calculus formation. Fear of permanent damage to the facial nerve has deterred surgeons from adopting a

similar attitude to the parotid gland; but if the main trunk of the nerve is identified before any dissection of the gland has been carried out, there should be no risk of permanent injury. Some temporary facial weakness due to handling of the nerve is possible, and the patient should be warned of this risk. The technique of total parotidectomy which has been followed has been described fully elsewhere (Eddey, 1951).

#### Summary.

1. The clinical features of recurrent parotitis are described. These comprise swelling and discomfort in one or other parotid gland persisting for days or weeks and recurring at intervals. X-ray investigation commonly gives negative results.

2. The usual methods of treatment are discussed briefly, and it is considered that they are unsatisfactory in preventing recurrences. Massage, dilatation of the duct, instillation of antibiotics and X-ray therapy may lessen the severity and frequency of attacks.

3. Two severe cases are reported in which cure was effected by total parotidectomy.

4. It is suggested that total parotidectomy should be considered in cases of unilateral parotitis in which frequent and severe attacks, unrelieved by other measures, are causing prolonged disability.

#### References.

- BIGLER, J. A. (1946), "Symposium on Pediatrics; Recurrent Parotitis", *M. Clin. North America*, 30:97.  
EDDEY, H. H. (1951), "Subtotal Parotidectomy for Mixed Salivary Tumour", *Australian & New Zealand J. Surg.*, 21:13.

### Reports of Cases.

#### CHICKEN-POX PNEUMONIA AND ENCEPHALITIS TREATED WITH AUREOMYCIN, WITH RECOVERY.

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CHICKEN-POX is usually considered as one of the mildest of the infectious diseases of childhood, and one in which recovery can be confidently predicted. Although encephalitis is well known as a possible complication of chicken-pox, cases are comparatively rare. It is not commonly realized that pneumonia is a commoner complication of chicken-pox than is encephalitis. The impression given by most standard text-books is that when pneumonia does occur it is commonly due to the aspiration of septic fluids arising from ulceration of the pharynx secondary to pharyngeal vesiculation. It does not seem to be appreciated that more commonly the pneumonia associated with chicken-pox is of virus type, and presumably due to the invasion of the lungs by the virus of chicken-pox. That there are pathological grounds for this belief is shown in several reports of a general dissemination of chicken-pox lesions in fatal cases of chicken-pox that have come to autopsy. Thus Oppenheimer (1944) has described a case of congenital varicella in a premature infant who died at the age of eleven days, with widespread visceral areas of necrosis and typical intracellular inclusions in the lungs, the bronchioles and many viscera. Johnson (1940) has described similar areas of focal changes in many viscera (although the lungs and pleura were unaffected) in a child who died in the acute phase. Claudy (1947) described scattered flat nodular lesions, about three to eight millimetres across, raised above the surface, over the pleural surfaces of the lungs in his fatal case. He stated that these were "apparently varicella pocks on the pleura", and that there were similar lesions within the pulmonary tissue and in the peripheral parts of the liver and spleen, which were histologically similar in structure.

These cases of "chicken-pox virus pneumonia" have been recorded more commonly in young adults than in subjects in other age groups, and in the past have shown a high fatality rate. Despite the fact that there is little evidence of a response of patients with ordinary chicken-pox to the use of antibiotics, there is a number of records of dramatic improvement after their use in the more severe complications of chicken-pox. This article records the concurrence of several complications in one case of chicken-pox, and a dramatic recovery after the use of aureomycin.

#### Clinical Record.

A man, aged twenty-three years, by occupation a motor truck driver for a firm of general carriers, was admitted to the Repatriation General Hospital, Springbank, South Australia, on July 28, 1950. He had been born in Alberton, South Australia. According to his own statement, his birth had apparently been a difficult one. His mother was ill for some time after he was born, and initially he was cared for by his grandmother. After birth "one eye looked up and the other down, and the mouth was twisted". At the age of five or six years his tonsils were removed. At the age of twelve or thirteen years he suffered an attack of mumps, with no history of any unusual features. He said that, prior to his present admission to hospital, he had had seven attacks of pneumonia, the first of these having occurred at the age of twelve months, and the last two years previously, when he was aged twenty-one years. He said that the attacks of pneumonia were diagnosed by doctors, the last attack having been treated with white tablets, which he imagined were "sulpha" tablets; but the details of these attacks were rather vague. He had been successfully vaccinated at the age of eighteen years, as a member of the Royal Australian Air Force. He had suffered from hæmorrhoids first at the age of nineteen years, and continued to suffer from this complaint until a hæmorrhoidectomy was performed at this hospital, under a spinal anaesthetic, on July 7, 1950. Pain developed at the site of the lumbar injection one or two days after the operation; he also developed some cough with a little sputum about the same time. An X-ray examination of the chest made on July 5, 1950, revealed no abnormality. On the evening of July 9 a course of penicillin injections, 50,000 units every three hours, was instituted and continued until July 11. On July 17 he was discharged from hospital, feeling well except for a slight ache at the site of the spinal injection, to recommence work on July 23. He was admitted to this hospital in the late morning of July 28, 1950. He had been at work as a motor truck driver on the morning of July 27, when he felt dizzy and nauseated, and had a headache. His throat felt sore, and he noticed some lumps in the neck. He had a small amount of cough with a little yellow sputum. There was no rash, neck stiffness, watering of the eyes or other symptoms. He continued working until the end of the afternoon. On July 28 he felt worse, and complained of thoracic pain. His local doctor was called to see him, and noted an increase of the breath sounds with bronchial breathing on the right side of his chest, and diagnosed the illness as early pneumonia, or possibly hepatitis. During the morning he was admitted to hospital, under my care.

Physical examination revealed the patient to be a lean young man with a flushed face, a temperature of 100° F. and a pulse rate of 100 per minute. His pupils were equal and reacted to light and accommodation. The tongue was furred, the fauces were reddened. His axillary and upper cervical lymph glands were enlarged, easily palpable, and tender. There was no neck stiffness. His chest moved evenly on respiration. The heart sounds were normal. The blood pressure was 135 millimetres of mercury, systolic, and 85 millimetres, diastolic. Increased breath sounds were heard at the lung bases posteriorly, but there were no adventitious sounds, and the percussion note and vocal resonance were normal. No abnormality was noticed in his trunk, limbs, or genitalia. His knee jerks and ankle jerks were equal and active; his plantar reflexes were flexor in type. Examination of his urine revealed a trace of albumin.

He was reexamined early in the afternoon, and it was noted that vesicles with a surrounding zone of erythema had appeared over his abdomen and back; they were typical of chicken-pox, and such a diagnosis was confidently made. Blood examination on this day gave the following information: the hæmoglobin value was 14.5 grammes per 100 millilitres, and the white cells numbered 5900 per cubic millimetre, 78% being neutrophile cells, 14% lymphocytes, and 8% monocytes. In the blood film the red cells appeared normal, while the neutrophile cells showed a shift to the left.

On the following day, July 29, the third of his illness, he was feeling a little better. The breath sounds were still harsh to auscultation. Further vesicles had appeared over his trunk.

On July 31 (fifth day) he was still pyrexial. The face and the rest of the body were now covered with vesicles. His cough had increased. The breath sounds were still harsh to auscultation, and a few rales were heard at the base of the left lung posteriorly. He did not feel so well. With a portable X-ray machine a picture was taken of his chest in the early afternoon; it showed "streaky nodular opacities scattered throughout both lungs and consistent

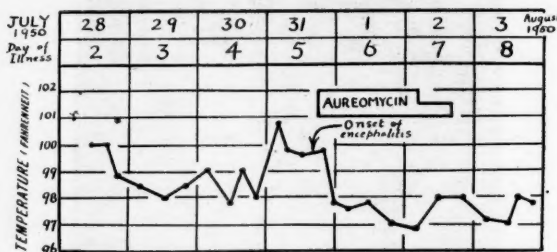


FIGURE 1.

Temperature chart from the case recorded.

with a virus pneumonia" (Dr. P. W. Verco). During the afternoon (of the fifth day of the illness) he became sleepy, confused and stuporose. A considerable degree of meningismus developed. He was diagnosed as suffering from chicken-pox with encephalitic involvement, and associated bronchopneumonia. As the pneumonia was of virus type, and as his symptoms were severe, he was treated with aureomycin, by mouth, 500 milligrammes being given every six hours for thirty-six hours, then 250 milligrammes every six hours for a further twelve hours, a total of four grammes over forty-eight hours.

On the following morning, the sixth day of his illness, his condition was considerably improved. There was now no evidence of any confusion, except that he had lost one complete day from his reckoning. He could not remember anything that had happened on the previous day. He spoke rationally and without difficulty. There was no longer any neck stiffness. Most of the vesicles were drying and the zone of erythema surrounding the vesicles was less.

On August 2, 1950 (the seventh day of his illness), the vesicles had become pustular, and the surrounding bands of erythema were two or three millimetres wide, as compared with the previous figure of five or six millimetres. No fresh vesicles had appeared, and not a single vesicle remained clear. The rash was now predominantly on the face and trunk. The buttocks, the lower part of the abdomen, the thighs, the legs and the arms were fairly free from vesicles. The patient had scratched the tops off many of his residual vesicles, and black eschars were present. There was no abnormality in the response of his pupils to light and accommodation. In the fauces only a little injection was apparent. Generalized lymphadenitis was present, but now the lymph glands were firmer and less tender than a few days before. The occipital lymph glands were not palpable. The cervical lymph glands were smaller than previously, firmer, still easily palpable, but

only just tender. The axillary lymph glands were firm, discrete and still tender. The epitrochlear glands were doubtfully palpable and just tender. The inguinal glands were palpable, firm and discrete, and only one of them was tender. The heart sounds were normal. There was some cough, with purulent sputum, yellowish with a greenish tint. The respiratory excursion was normal. There was some dullness to percussion at the bases of the lower lobes of the lungs posteriorly, the percussion note being natural elsewhere over the lungs. The breath sounds were still harsh. There were no adventitious sounds to auscultation. The reflexes were unchanged. He complained of feeling "a little giddy" on sitting up. He had still no recollection of having been examined radiologically on July 31, nor had he subsequently. A further X-ray film of the lung fields was taken on August 2, the radiologist reporting that "some resolution has occurred". Photographs of the skin rash were also taken.

On August 3 (eighth day) he felt very much better, and was sitting up in bed, whistling, when I saw him. No further vesicles had developed, and only one or two vesicles still remained pustular. The blood was reexamined. The haemoglobin value was 14.8 grammes per centum. The white cells numbered 7300 per cubic millimetre, 51% being neutrophile cells, 38% lymphocytes, 7% monocytes, and 4% eosinophile cells. Examination of the lymphocytes revealed mainly a deeply basophilic cytoplasm, and about a quarter of the lymphocytes were immature, with nuclei showing compact chromatin and one or three nucleoli. One such cell was seen in division. The Wassermann, Kline and Berger-Kahn tests all produced negative results. Some serum was preserved for further serological studies.

On August 4 he felt well. A lumbar puncture was performed. The cerebro-spinal fluid was clear and colourless. The pressure was 110 millimetres of water. The response to Queckenstedt's test was normal. Microscopic examination of the fluid revealed no cells. The protein content was 22 milligrammes per 100 millilitres, and there was no excess of globulin. The chloride content was 750 milligrammes (as sodium chloride) per 100 millilitres, and the glucose content was 71 milligrammes per 100 millilitres; the colloidal gold test showed no precipitation of the gold sol in dilutions of the cerebro-spinal fluid from one in 10 to one in 5120.

From August 5 until his discharge from hospital on August 14 he felt well, except for a few headaches. There was no further development of vesicles. His chest was radiologically examined on August 5 (postero-anterior view) and on August 7 (right lateral view), and on each of these examinations the radiologist reported: "The lungs now appear clear." He reported back for a further serum specimen to be taken on August 28.

On July 20, 1951, he reported back to me for further blood specimens to be taken. About 30 millilitres of blood were taken with a syringe from the right antecubital vein, with the patient seated. About two minutes after the completion of this process, which was without difficulty, he complained of feeling dizzy, and became limp. I held his head to prevent its falling back on the chair. Suddenly his head shot back hard, hitting a wooden partition immediately at the back of his chair with a loud whack. His arms then rose (abducted) to the level of his shoulders, with the elbow bent to a right angle, the palms facing forwards, the hands semiflexed. His arms immediately showed a coarse tremor, mainly in the hands and forearms. His body then slid forward out of the chair, his legs being flexed behind his thighs. He slumped to the floor, where he remained unconscious for about fifteen minutes; he vomited on recovering, and after about three hours felt well enough to go home unaided. There had been no apnoea, micturition, tongue-biting or cyanosis.

He stated after recovery that he had had several "black-outs" while driving his truck at his normal occupation, but that these attacks always gave him sufficient warning for him to stop his vehicle in time to avoid any accident. He stated that he usually "keeled over" with injections or venepuncture. As the fit was very suggestive of "reflex

epilepsy", he was readmitted to hospital on August 27, 1951, for further investigation.

He said after his admission that he had had "giddy attacks" for about five years. These would start with a "buzz in the ears" sounding like the "steam chuffing from a train while it is waiting at the station". After about two minutes he would feel giddy, and would go and sit down until he recovered. These "giddy attacks" would occur once in every eight or ten days on the average.

In addition to the giddy turns with their auditory aura, he suffered from occasional fainting attacks without any aura, about once every five weeks, these being brought on by exertion, such as loading or unloading his vehicle. He distinguished his "fainting attacks" sharply from his "giddy turns". There was a family history that his mother was a nervous woman.

Physical examination of the patient revealed no abnormality in his cardio-vascular, respiratory or nervous system. The blood pressure was 110 millimetres of mercury, systolic, and 80 millimetres, diastolic. Examination of his urine revealed no abnormality. His skin had many small scars where his chicken-pox vesicles with their subsequent eschars had been. The chest X-ray film showed no abnormality. The haemoglobin value was 15.8 grammes per centum. The white cells numbered 11,500 per cubic millimetre, 73% being neutrophile cells, 22% lymphocytes, 2% monocytes, 2% eosinophile cells and 1% basophile cells. Venepuncture with the patient lying in bed did not produce a fit. It was not possible to have an electroencephalographic examination made.

The diagnosis was considered to be epilepsy with an auditory aura, with tendencies to reflex epilepsy. Similar attacks of "reflex epilepsy" following injections have been recorded by Bell (1952) and by Webster (1952). It did not appear that his epilepsy had any relationship to the chicken-pox attack of twelve months before. He was treated with "Dilantin", one and a half grains three times a day, and within two days was losing a lot of his "giddy feelings" and was much improved within a week. Whilst he has continued with this therapy, he has been free from his "giddy attacks".

#### *Differential Diagnosis of the Exanthem.*

On clinical grounds there was little doubt that the patient was suffering from chicken-pox. The vesicles were characteristic of this disease. However, the concurrence of several rare complications in one case—pneumonia, encephalitis and lymphadenitis—causes one to consider possible alternatives in diagnosis. Each of these complications will be discussed separately later. It is regretted that a biopsy was not performed on a vesicle during the course of the illness, as the histological features would have been practically diagnostic. Further support or otherwise for the diagnosis was sought in epidemiological and serological considerations.

#### *Epidemiological Considerations.*

The patient had had no previous attack of chicken-pox or shingles, nor could any history of recent contact with either of these complaints be found. In his job he came in contact with many people. During the eleven to twenty-one days prior to the onset of his symptoms he was in hospital for a haemorrhoidectomy, but again visitors frequently visited the ward. There was no record of any chicken-pox to be found in his contacts. Hence no conclusions can be drawn either way from his history of human contacts.

Three days prior to the onset date of July 27, 1950—that is, July 24—there was a fire in a neighbour's garage (at Ethelton, South Australia), which had been used as an unhygienic dwelling place by an old couple, and since that date many rats and mice had appeared in his house. There is a mouse-borne disease, rickettsialpox, which resembles chicken-pox clinically, but which so far has been described from only a limited region of North America. Fortunately, serological aids can be used in the diagnosis of this disease, as well as in chicken-pox, and were used to exclude the former, as well as to confirm the diagnosis of chicken-pox.

TABLE I.  
Result of Complement-Fixation Tests on Specimens of Serum from the Acute and Chronic Stages of the Illness.

Specimen of Serum.	Titre.					Serum Control. (Titre 1/5.)	Antigen Control.
	1/5	1/10	1/20	1/40	1/80		
Serum of August 3, 1950	0	—	—	—	—	0	0
Serum of August 28, 1950	++++	+++	+	0	0	0	—

#### Serological Considerations.

Specimens of serum taken during the acute and convalescent stages of the illness were submitted to Dr. J. A. R. Miles, of Adelaide, who performed a chicken-pox complement fixation test on them. The results were as shown in Table I.

Dr. Miles reported as follows:

I take the titre of the serum of 28/8/50 as 1/10, and in view of the long storage of the serum (10 months) under conditions far from ideal, the fact that the antigen being used was not very good, and the fact that the acute specimen showed no trace of complement fixation activity at 1/5, I think that the result strongly suggests that the patient was suffering from chicken-pox.

The only possible source of error is that material from rickettsialpox may have been included in the antigen, but I think that this is unlikely as all the material (fluid from chickenpox vesicles) came from typical cases in the present epidemic of chickenpox in South Australia (June, 1951).

Agglutination tests (Well Felix) of the serum against suspensions of Proteus OX19, OX2 and OXK gave negative results. It was considered that an attempt to exclude any known rickettsiosis by further serological studies should be made, so the remainder of the specimens of serum, as well as some fresh specimens preserved with "Merthiolate" (one in 1000), were sent to Dr. E. H. Lennette, of San Francisco, United States of America, for study. Dr. Lennette reported as follows on the specimens taken on August 3, 1950, August 28, 1950, and July 21, 1951: "The complement fixation tests for Q fever, typhus fever, and for the spotted fever group (Rocky Mountain spotted fever and rickettsialpox) were negative."

On all the grounds, therefore, it was considered that the evidence was in favour of a diagnosis of chicken-pox with various unusual complications, and that there was no evidence in favour of any other diagnosis.

#### Discussion of the Clinical Features.

##### Encephalitis.

The evidence in favour of encephalitis was that, on the afternoon of the fifth day of the illness, the patient became confused and stuporose, and considerable neck stiffness was present. A lumbar puncture was not performed until the ninth day, when examination of the cerebro-spinal fluid revealed no abnormality.

The most extensive review of encephalitis from chicken-pox is due to Underwood (1935), who recorded the clinical and other features of 119 cases of chicken-pox encephalitis culled from the literature. This author classified the clinical types of involvement of the nervous system into five groups which tend to overlap a good deal. Thus his Group 1 is "meningo-encephalitis", and Group 2(a) is "cerebral encephalitis"; yet in both of these groups there may be dulling of the intellect, stupor, or even complete coma, and meningeal signs. Underwood reviewed the findings on 58 lumbar punctures. The pressure of the cerebro-spinal fluid was normal in 20 of the 42 in which this feature was recorded, in 10 it was slightly increased, and in 12 there was a considerable increase. The cell count was recorded in 55 cases, being normal in 31, slightly increased in 20, and greatly increased (80 or more cells per cubic millimetre) in only four cases; of these cases in which there was an increased cell count,

the lymphocytes or mononuclear cells predominated in nearly all. The protein content was recorded in 40 cases, being normal in 31, and greatly increased in nine.

With regard to prognosis, Underwood recorded that 12 patients died out of 109, 80 recovered completely, and 17 showed some sequelae after recovery. Thus we may expect that about two-thirds of patients who suffer from chicken-pox encephalitis will recover completely.

According to Stokes (1947), encephalomyelitis is usually recorded "toward the end of the febrile period but may appear from one to three weeks following an attack of the disease". According to Gunn (1950), encephalomyelitis occurs at intervals from "7-14 days from the onset of the varicella". Van Rooyen and Rhodes (1948) state that in the great majority of cases of nervous involvement in chicken-pox it develops four to ten days after the onset. Although these accounts vary, the onset of the encephalitic symptoms in the case presented here, on the fifth day, although comparatively early is not unusually so. Despite the considerable number of cases recorded by Underwood and by others, encephalitis still appears to be a rare complication of chicken-pox. Bullowa and Wishik (1935) record only five cases of encephalitis in 2534 cases of chicken-pox—an incidence of 0.2%.

##### Pneumonia in Chicken-pox.

Bullowa and Wishik (1935), in their account of the complications of chicken-pox, record 21 cases of pneumonia in 2534 cases of chicken-pox—an incidence of 0.8%. There were 11 fatal cases in this series; but these authors state that in only one case was pneumonia a cause of death, and that in a case complicated by septicæmia. Further details of this case are not given. Three cases of pneumonia were complicated by empyema. Dolgopol (1942) has given some further information on eight of the 11 fatal cases mentioned, in a communication to Waring *et alii* (1942). According to Dolgopol, "slight to severe lobular pneumonia was evident at post-mortem examination". One patient was aged thirty years; all the others were children under six and a half years. Dolgopol stated that in no case was the pneumonia of peribronchial type.

Millous (1936) recorded an outbreak of 1919 cases of chicken-pox, with 370 deaths, mostly in adults, in the French Cameroon district in 1935. Death in the fatal cases was stated to have been due to nephritis and uræmia, or to severe laryngitis with prominent dysphagia and dyspnoea. Mitchell and Fletcher (1927) had recorded four cases of complicating bronchopneumonia in a series of 775 patients suffering from chicken-pox admitted to the Cincinnati General Hospital over the period from 1913 to 1926.

Waring *et alii* (1942) record a fatal case of chicken-pox in a man, aged forty years, with acute bronchopneumonia, hæmoptysis, encephalitis and nephrosis, and give a description of the post-mortem examination. In the same article they record another case, that of a man, aged thirty-three years, with acute bronchopneumonia, profuse bright bloody sputum, dyspnoea, cyanosis, delirium, and moderate nitrogen retention, with recovery. These authors appear to be the first to suggest that chicken-pox virus pneumonia can occur. Rausch *et alii* (1943) record the case of a man, aged thirty-three years, with pneumonia of "atypical" or bronchopneumonic type in chicken-pox, with laryngeal spasm, dysphagia and cyanosis, with recovery. Claudy (1947) recorded a fatal case of chicken-pox in a woman

aged thirty-two years, with pneumonia. The X-ray film in this case revealed a homogeneous dense area in the lower half of the left lung, and a diffuse bronchopneumonic type of infiltration throughout the remainder of the lung fields. As was recorded earlier, pock-like lesions were present in the pleura, lungs, liver and spleen. Grayson and Bradley (1947) have recorded a case of chicken-pox pneumonia and nephritis in a man, aged thirty-four years, with recovery. On his admission to hospital, clinically the only abnormal feature related to his lungs was a constant dry cough. An X-ray examination of the chest at the same time (four days after the onset) revealed a few "scattered, small, scarcely visible densities". His cough became more severe, and fine crackling râles developed at the base of the right lung posteriorly, and later wheezes and râles were heard over the entire chest. At this stage the X-ray film of the chest revealed diffuse finely nodular infiltrations throughout both lung fields. He gradually recovered. In the early stages of his illness he was treated with sulphadiazine without relief, and later with penicillin without any great relief. Bunn and Hammond (1950) record two similar cases; the first of a woman, aged thirty years, with bronchopneumonia in chicken-pox; the second that of a man, aged thirty years, with "overwhelming pneumonia"; both of these "morbidly ill" patients responded well to treatment (see later). Gunn (1950) records that terminal bronchopneumonia can occur as a complication of *varicella gangrenosa* in debilitated children, with sloughing ulcers, possibly complicated by measles or scarlet fever.

One could expect aspiration pneumonia of lobar type to follow the sloughing pharyngeal ulceration which occasionally occurs; but from the evidence available it would appear that pneumonia in chicken-pox is much more commonly of bronchopneumonic type, and can reasonably be ascribed to chicken-pox virus pneumonia.

Various bacteria have been isolated by sputum culture or other means in these cases of chicken-pox pneumonia. Thus Bullova and Wishik (1935) isolated in their cases what they believed to be the causative organisms of the pneumonias associated with chicken-pox. These were "almost invariably a *Streptococcus*; *S. haemolyticus* more frequently than *S. viridans*". Waring *et alii* (1942) isolated a pneumococcus from the sputum of their first patient, and in their second case a haemolytic streptococcus, later identified as *Streptococcus anginosus*. However, they record that at the autopsy on their first case bacteria were rare or absent, only an occasional Gram-positive diplococcus being present in the pulmonary tissue. These authors were of the opinion that their first case of pneumonia was due to chicken-pox virus. Their second patient responded rapidly to "convalescent streptococcus serum", and they were not prepared to discount entirely the role of a secondary invasive bacterial flora in the causation of the pneumonic symptoms. Grayson and Bradley (1947) record that in their case of chicken-pox pneumonia and nephritis "examinations of sputums were negative, except for normal flora in the respiratory tract. Pneumococci or haemolytic streptococci were not found". In Claudy's (1947) case a mixed culture was obtained of streptococci, staphylococci, micrococci and a type IV pneumococcus, which was believed to be a mouth contaminant. Bunn and Hammond (1950) record that in their first case single cultures from blood, from sputum, and from the throat gave negative results.

In the case presented in this paper, yeast organisms were isolated from the sputum on two occasions, after the use of aureomycin. These were *Monilia albicans*, identified by staining and culture; they were not considered of any pathological significance. No other organisms were found in the sputum. It is interesting to note the incidence of *Monilia* infections after the use of modern antibiotics; for example, Woods *et alii* (1951) have recorded a number of cases of monilial overgrowth in the oro-pharynx and elsewhere in association with aureomycin or other antibiotic therapy given orally and parenterally.

#### Lymphadenitis.

Lymphadenitis is unusual in an ordinary case of chicken-pox. In the more severe cases of chicken-pox it is not rare, and appears to be largely due to secondary infection once the vesicles have been ruptured. Stokes (1947) thus records occipital and posterior cervical lymphadenitis from secondary infection of ruptured chicken-pox vesicles of the scalp. Bullova and Wishik (1935) record lymphadenitis as one of the commoner complications of chicken-pox—16 cases in their series of 2534 cases—an incidence of 0.6%.

It is to be noted that in the case presented here the lymphadenitis was present and generalized at the first examination, on the second day of the disease, and prior to the appearance of the vesicles, and hence could not have been due to secondary infection.

#### Chicken-pox with Involvement of Multiple Systems (Disseminated Chicken-pox).

The occasional occurrence of cases of chicken-pox with multiple system involvement has led some authors to use the term "disseminated chicken-pox", which is quite justifiable on pathological grounds. In fact, in the more severe cases of the disease widespread lesions may occur, including some in internal organs, as has been mentioned earlier. Renal involvement may occur, there being a number of cases of nephritis and nephrosis on record (for example, Henoch, 1884; Denny and Baker, 1929; Tilley and Warin, 1938; Waring *et alii*, 1942; Gill, 1942; and Grayson and Bradley, 1947). Despite these records, renal involvement in chicken-pox appears to be rare. Mitchell and Fletcher (1927) recorded only one case of renal involvement (a case of nephritis) in their series of 775 cases. Bullova and Wishik (1935) do not record a single case of renal involvement in their series of 2534 cases of chicken-pox.

In the case recorded here there was no evidence of any renal involvement, beyond the recording of a trace of albumin in the patient's urine on his admission to hospital, to which no great significance is attached.

#### Response of Chickenpox Pneumonia to Treatment.

There does not appear to be much good evidence that any of the antibiotics in common use have any effect upon uncomplicated chicken-pox. Thus Mazursky *et alii* (1950) were not able to observe that patients suffering from chicken-pox treated by aureomycin given orally showed any better response than untreated controls. Dowling *et alii* (1949) similarly were unable to see any benefit from the use of aureomycin in chicken-pox. On the other hand, some reports have been rather more favourable; thus Kalz *et alii* (1949) have reported rapid drying of the vesicles of chicken-pox and *herpes zoster* with the topical application of aureomycin in an adherent film of water-soluble methyl cellulose—"marked differences were observed" in the treated areas as against the untreated areas. Finland *et alii* (1949) have reported a beneficial action of aureomycin by mouth in *herpes zoster*—it gave relief of pain, and caused drying and healing of the vesicles; and Binder and Stubbs (1949) have also reported the rapid relief of pain and the drying of the vesicles in *herpes zoster* after oral aureomycin therapy.

Despite these varying reports on the value of aureomycin in ordinary cases of chicken-pox, the response in severe and complicated cases to the newer antibiotics appears to be almost universally favourable. Thus Anthony (1951) has reported the dramatic recovery of a man, aged thirty-five years, with the use of chloramphenicol therapy. This author stated that this was the severest case of chicken-pox that he had seen in twenty years of general practice. Bunn and Hammond (1950) treated with aureomycin two morbidly ill patients suffering from chicken-pox with associated initial pneumonia. There was a striking recovery in each case. In the first case, however, aureomycin, streptomycin, penicillin and chicken-pox convalescent serum were given as a combined treatment, so the striking improvement was not necessarily due to the aureomycin; but in the second case, aureomycin alone,

given by mouth, was used, and there was a prompt crisis, the temperature dropping from 105° F. to normal in a few hours. These authors were so impressed that they subsequently treated seven patients with uncomplicated chicken-pox with a trial of aureomycin given parenterally and orally. Two adults of this series of seven had no further skin involvement after commencing this therapy, but in the remaining five cases (two adults and three children) new vesicles continued to appear for as long as three or four days. These authors stated that in none of these seven cases was there a "truly impressive response".

Waring *et alii* (1942) treated their first patient (who died) with sulphathiazole; their second patient was treated with sulphathiazole, later changed to sulphanilamide, digitalis, and convalescent streptococcus serum. They record that in this second case the "extremely sore throat" was completely relieved after the first injection of this serum. The patient of Rausch *et alii* (1943) showed a good response after sulphathiazole therapy. Claudy's (1947) patient was unsuccessfully treated with sulphadiazine, convalescent serum and digitalis. Grayson and Bradley's (1947) patient showed no improvement with sulphadiazine, but gradual improvement after this was changed to penicillin, although the temperature remained elevated.

In the case presented in this article, the response to oral aureomycin therapy was dramatic. The encephalitis and pneumonia disappeared, and the gravely ill patient rapidly became well. No further vesicles appeared upon the skin, and the existing vesicles regressed rapidly.

The statement of Bunn and Hammond (1950) appears to be very apt: "It is not claimed that aureomycin is a specific antiviral agent in varicella, but its use in fulminating and complicated cases is warranted." The exact mechanism of this therapy is not clear; aureomycin does not appear to be the only "trigger mechanism" which will turn the scale. Of the antibiotics available, aureomycin appears to be the most suitable at the present time.

#### Summary.

A case of chicken-pox complicated by encephalitis, bronchopneumonia and lymphadenitis in a man, aged twenty-three years, is presented. The presence of the pneumonia was suspected from the onset, prior to the appearance of vesicles, and confirmed by X-ray examination on the fifth day, after more pronounced symptoms and signs had appeared. It is considered that the pneumonia was of virus type and due to the virus of chicken-pox. Lymphadenitis appeared within twenty-four hours of the onset of the illness, and prior to eruption of vesicles. Encephalitis became evident on the fifth day.

Treatment with aureomycin by mouth was instituted on the fifth day, and continued over a forty-eight hour period. On the sixth day the patient's condition was considerably improved. His stupor and meningismus had gone, his vesicles were drying, and no fresh vesicles appeared subsequently. The vesicles finally progressed to multiple small black eschars with eventual scarring. The evidence of the pneumonia rapidly disappeared. The convalescence was uninterrupted. The diagnosis of chicken-pox was confirmed by complement-fixation tests.

Complications of chicken-pox are discussed, particularly pneumonia, encephalitis and lymphadenitis. The therapy of chicken-pox pneumonia is discussed. Although there is little evidence that aureomycin or other antibiotics have any effect on ordinary chicken-pox, there are a number of records of dramatic improvement in severe or complicated chicken-pox, and in view of the high fatality rate of the earlier recorded cases of chicken-pox pneumonia, a trial of aureomycin therapy appears worth while in chicken-pox complicated by pneumonia.

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#### References.

- ANTHONY, E. (1951), "Chicken-pox and Chloramphenicol", *Brit. M. J.*, 1: 414.
- BELL, R. (1952), "Epilepsy After an Injection", *Lancet*, 1: 1072.
- BINDER, M. L., and STUBBS, L. E. (1949), "Treatment of Herpes Zoster with Aureomycin", *J.A.M.A.*, 141: 1050.
- BULLOWA, J. G. M., and WISHIK, S. M. (1935), "Complications of Varicella", *Am. J. Dis. Child.*, 49: 923.
- BUNN, P. A., and HAMMOND, J. D. (1950), "Chickenpox Complicated by Severe Pneumonia Treated with Aureomycin", *New York J. Med.*, 50: 1485.
- CLAUDY, W. D. (1947), "Pneumonia Associated with Varicella", *Arch. Int. Med.*, 80: 185.
- DENNY, E. R., and BAKER, E. M. (1929), "Varicella Complicated by an Acute Nephritis", *Bull. Johns Hopkins Hosp.*, 44: 201.
- DOLGOROPOL, V. P. (1942), Personal Communication to Waring *et alii* (1942), *loco citato*: 385.
- DOWLING, H. F., LEPPER, M. H., CALDWELL, E. R., WHELTON, R. L., and SWEET, L. K. (1949), "Aureomycin in Various Infections: Report of One Hundred and Eighty Cases and Review of the Clinical Literature", *M. Ann. District of Columbia*, 18: 335.
- FINLAND, M., FINNERTY, E. F., COLLINS, H. S., BAIRD, J. W., GOCKE, T. M., and KASS, E. H. (1949), "Aureomycin Treatment of Herpes Zoster", *New England J. Med.*, 241: 1037.
- GILL, D. (1942), "Nephritis as a Complication of Varicella", *Arch. Pediat.*, 59: 587.
- GRAYSON, C. E., and BRADLEY, E. J. (1947), "Disseminated Chickenpox (Pneumonia and Nephritis)", *J.A.M.A.*, 134: 1237.
- GUNN, W. (1950), "Chicken-pox", in "The British Encyclopedia of Medical Practice", Second Edition, 3: 378.
- HENoch, E. (1884), "Nephritis nach Varicellen", *Berliner klin. Wchnschr.*, 21: 17.
- JOHNSON, H. N. (1940), "Visceral Lesions Associated with Varicella", *Arch. Path.*, 30: 292.
- KALZ, F., PRICHARD, H., and SURKIS, S. Z. (1949), "Aureomycin Film in Topical Treatment of Cutaneous Virus Eruptions", *Canad. M. A. J.*, 61: 171.
- MAZURSKY, M. M., WRIGHT, L., and WEICHEL, M. (1950), "Clinical Observations on the Use of Aureomycin in Varicella", *Pediatrics*, 5: 276.
- MILLOUS (1936), "Une épidémie de varicelle maligne au Cameroun", *Bull. Acad. de Méd. Paris*, 115: 840.
- MITCHELL, A. G., and FLETCHER, E. G. (1927), "Studies on Varicella, Age and Seasonal Incidence, Recurrences, Complications and Leukocyte Counts", *J.A.M.A.*, 89: 279.
- OPPENHEIMER, E. H. (1944), "Congenital Chickenpox with Disseminated Visceral Lesions", *Bull. Johns Hopkins Hosp.*, 74: 240.
- RAUSCH, L. E., GRABLE, T. J., and MUSSER, J. H. (1943), "Atypical Pneumonia Complicating Severe Varicella in an Adult", *New Orleans M. & S. J.*, 96: 271.
- STOKES, J. (1947), "Varicella", in "Cecil's Text Book of Medicine", Seventh Edition: 33.
- TILLEY, J. B., and WARIN, J. F. (1938), "A Severe Case of Chicken-pox with Some Unusual Features", *Brit. M. J.*, 1: 1265.
- UNDERWOOD, E. A. (1935), "The Neurological Complications of Varicella: A Clinical and Epidemiological Study", *Brit. J. Child. Dis.*, 32: 83, 177, 241.
- VAN ROOYEN, C. E., and RHODES, A. J. (1948), "Virus Diseases of Man", Second Edition: 272.
- WARING, J. J., NEUBERGER, K., and GEEVE, H. F. (1942), "Severe Forms of Chickenpox in Adults with Autopsy Observations in a Case with Associated Pneumonia and Encephalitis", *Arch. Int. Med.*, 69: 384.
- WEBSTER, R. C. (1952), "Epilepsy After an Injection", *Lancet*, 1: 1165.
- WOODS, J. W., MANNING, I. H., and PATTERSON, C. N. (1951), "Monilial Infections Complicating the Therapeutic Use of Antibiotics", *J.A.M.A.*, 145: 207.

#### Books Received.

[The mention of a book in this column does not imply that no review will appear in a subsequent issue.]

"The Surgical Clinics of North America": 1953. Philadelphia and London: W. B. Saunders Company. Melbourne: W. Ramsay (Surgical), Limited. Lahey Clinic Number. 9" x 6", pp. 322, with 126 illustrations. Price: £7 5s. per year with cloth binding, and £6 per year with paper binding.

Contains 30 articles in a symposium on surgical lesions of the neck and upper part of the mediastinum.

"Incompatibility in Prescriptions and How to Avoid It: With a Dictionary of Incompatibilities", by Thomas Stephenson, D.Sc., Ph.C., F.R.S.E. Sixth edition, by James Burnet, M.A., LL.B. (London), M.D., F.R.C.P.E.; 1953. Edinburgh: "The Prescriber" Publishers, Limited 8½" x 5½", pp. 70.

The previous edition was issued in 1949.

## The Medical Journal of Australia

SATURDAY, NOVEMBER 7, 1953.

All articles submitted for publication in this journal should be typed with double or treble spacing. Carbon copies should not be sent. Authors are requested to avoid the use of abbreviations and not to underline either words or phrases.

References to articles and books should be carefully checked. In a reference the following information should be given without abbreviation: surname of author, initials of author, year, full title of article, name of journal without abbreviation, volume, number of first page of the article. If a reference is made to an abstract of a paper, the name of the original journal, together with that of the journal in which the abstract has appeared, should be given with full date in each instance.

Authors who are not accustomed to preparing drawings or photographic prints for reproduction are invited to seek the advice of the Editor.

### THE MENTAL HOSPITAL TREATMENT OF JUVENILES.

ALTHOUGH from time to time discussion has taken place on the mental treatment of juveniles in special institutions, very little has been done about it. There is no doubt that if adolescents suffering from abnormal mental conditions could be brought under treatment at an early stage, recovery would be much more likely to occur than it is when the young person is allowed to drift on until such time as he or she becomes certifiable for admission to a mental hospital. This means that treatment will have to be voluntarily sought. Reference to this subject is called for by the publication in *The Journal of Mental Science* of January, 1953, of a communication from Dr. D. E. Sands, physician-superintendent of St. Ebba's Hospital, Epsom, England. The title of his article is: "A Special Mental Hospital Unit for the Treatment of Psychosis and Neurosis in Juveniles". Sands begins his article with the statement that units of the kind which he is reporting are the development of a trend which has been going on for the past twenty-five years. Prior to 1930, patients were certified and admitted to mental hospitals when they were largely suffering from the end results of psychiatric illness. Since 1930 the voluntary system has brought many patients to hospital at a stage when their illness can be influenced favourably by modern methods of treatment. Fortunately, much of the stigma of mental illness has disappeared, and illness of the mind is looked on as not very different from illness of the body. It is commonly recognized that children or adolescents suffering from mental illness are not all suitable for treatment in a hospital intended for adults. Sands points out that until recently there has been no place where the mental illness of juveniles could be investigated and treated. A small percentage of the patients went to mental deficiency hospitals and others were sent to approved schools and various homes. Many, however,

were kept in their own homes until breakdown became so complete and obvious that they had to be admitted to the ordinary mental hospitals as occasional "teenagers" amongst a host of adults. Others again were simply retained at home until they were old enough to go to such hospitals. Sands states that the number of such admissions of juveniles for England and Wales totalled about 3000 a year. It is important to recognize that, during the juvenile period, there may be a psychiatric breakdown to a degree which, from the medical and social standpoint, presents as great a problem as does psychiatric illness in later life. Moreover, institutional treatment is quite as necessary for some juveniles as it is for some adults. St. Ebba's Hospital has created a juvenile unit comprising 25 male and 25 female beds. For information in regard to the general setting of the unit, the staffing and material facilities, Sands refers the reader to a paper by W. Warren published in *The Lancet* of January 19, 1952.

Describing his unit, which consists of two special wards in The Bethlem Royal Hospital and The Maudsley Hospital, Warren states that sixteen beds were available for boys and sixteen for girls between twelve and sixteen years of age. The regimen aimed at was intended to be helpful to the anxious, inhibited or aggressive patient. Both freedom and discipline are necessary, and the physician in charge was required to steer the whole ward—staff and patients—along a tolerant middle course. Adequate room indoors and out for activity, including "healthy horseplay", was important; damage could thus be kept well within bounds. Formal occupations included regular occupational therapy, daily physical exercises and organized games. Formal education was provided on an adequate scale, with regular and individual attention for the needs of each patient. The staff included a physician-in-charge for each ward, who supervised all aspects, administrative and clinical, and a registrar, adequately trained in child psychiatry as well as in adult psychiatry, in a personal and intimate relation with the patients in treatment. A psychiatric social worker was also employed. A mentally and generally trained nurse had charge of each ward, a male nurse being employed for boys. These all constituted a team, and met at regular intervals to pool their observations.

Turning again to St. Ebba's Hospital unit, we are justified in the view that with the set-up described useful work should be possible. It is to be noted that the majority of patients admitted as pre-psychotic did not turn out to be psychotic; if they did, the diagnosis was usually schizophrenia. It is interesting that only about half the patients sent for in-patient care because of the severity of their problems were placed in any of the main clinical groups—though nearly all had been referred to the hospital by psychiatric specialists. When diagnosis had been attempted, it stood the test of in-patient observation and full investigation in about two-thirds of the cases; schizophrenia tended to be over-diagnosed at the expense of neurotic, psychopathic and epileptic states. Among females particularly, some patients were referred to as schizophrenics, but subsequently proved to be suffering from hysteria. In view of the need for early treatment Sands regards it as satisfactory that so damaging a disease as schizophrenia was not often missed. Psychopathic personalities constituted just under one-third of all admissions. Many

patients had to be admitted for investigation in the first instance, since in the early stages of illness the only obvious feature might be some form of behaviour disorder. Sands regards it as unfortunate that the so-called deprived child or juvenile should be almost exclusively regarded as emotionally deprived or delinquent. The patients in the unit described by him are deprived in various fields, not only emotional, but intellectual, hereditary, social, material, endocrine and so on. At the same time he adds that an excess of growth, as well as of intellectual and emotional development, may be productive of breakdown. He refers to a paper by E. M. Widdowson, published in *The Lancet* of June 16, 1951, in which mental contentment and physical growth are discussed. One sentence in this paper is so important that it should be reproduced. Widdowson points out that even the most perfectly planned nutritional investigation may be ruined by psychological factors over which the investigator may have no control. He states that those about to embark on feeding experiments would do well to remember that: "Better is a dinner of herbs where love is, than a stalled ox and hatred therewith." When he describes his treatment carried out at St. Ebba's Hospital, Sands points out that the most important single factor in daily affairs is the sympathetic management by the nursing staff, who have to make suitable response, not only to many tokens of affection, but to occasional impulsive attacks.

At St. Ebba's Hospital all forms of psychiatric treatment appear to be used, even leucotomy. Short notes are given of four juvenile patients on whom this operation was performed. Sands gives some details of 217 patients who were discharged from the institution. Of this total, 46 suffered from schizophrenia; 12 recovered, 23 were improved, and in eleven cases no change occurred. Sixty-nine had psychopathic personalities; one recovered, 20 manifested improvement, and in 28 cases no change occurred. Forty-seven suffered from neuroses; 10 recovered, 33 manifested improvement, and in four cases no change occurred. Twelve suffered from organic states; one recovered, seven manifested improvement, and in four cases no change occurred. Twenty-three suffered from epilepsy; one recovered, 18 manifested improvement, and in four cases no change took place. Fourteen suffered from affective psychoses; six recovered, seven manifested improvement, and in one case no change occurred. Six suffered from mental defect; there were no recoveries, four manifested improvement, and in two cases no change took place. The totals for the 217 patients are 31 recoveries, 132 improvements, and 54 with no change. In this list, as far as possible, cases with doubtful diagnoses have been omitted. Sands remarks that because of the poor prognosis generally attached to juvenile schizophrenia, the results in this condition are of interest and are to some extent to be accounted for by the acute cases in which the prognosis was more favourable. It will be clear that if these patients had not been admitted to a mental hospital while they were young, many of the recoveries and much of the improvement would not have occurred.

The conclusion to be drawn from this interesting account given by Sands of his unit at St. Ebba's Hospital is that special mental hospitals or special units for juvenile patients to be treated on a voluntary basis are a step in the right direction. Their establishment in all mental

hospital services is surely indicated. The two points to be remembered are that the patients come under treatment in the early stages of their illness, and that they come on a voluntary basis, which means that there is more hope for them than could otherwise be entertained.

## Current Comment.

### WORKING AT NIGHT.

SURPRISINGLY little attention has been paid to the industrial hygiene aspects of working on night shifts. It is unavoidable in certain industries and occupations, but those who have to engage in it generally dislike it. Official industrial regulations are mostly designed to discourage it or to forbid it when it is not essential, but comparatively little seems to have been done to define the factors involved. An interesting contribution to the subject comes from England in a paper by S. Wyatt and R. Marriott,<sup>1</sup> from the Medical Research Council Group for Research in Industrial Psychology. Wyatt and Marriott state that objections to night work have been made on medical, social and economic grounds, and that the last of these aspects was studied in some detail by the Health of Munition Workers Committee during the 1914-1918 war. This committee found no significant difference between the rates of output of men employed on alternate day and night shifts and recommended this system in preference to continuous night work. Alternate day and night work was also shown to be only slightly inferior, as regards output, to continuous day work, while from the standpoint of lost time it was better than day work. These findings, Wyatt and Marriott point out, refer mainly to a weekly change of shifts, but in many factories shifts are changed every fortnight and in some every month. Figures collected by Vernon in 1917 for the Health of Munition Workers Committee showed that when shifts were changed fortnightly, output was slightly higher and absenteeism less during the first week of the night shift than during the second. The corresponding figures for the day shift showed, if anything, the opposite tendency.

It seems clear that there are both physiological and psychological factors to be considered in the question of night work, and adaptation is not a simple matter. Variations in temperature throughout the twenty-four-hour period are a well-known physiological phenomenon. Best and Taylor state that a difference of 0.5° F. or even 1.0° F. occurs between the maximum in the late afternoon or early evening and the minimum at about four or five o'clock in the morning, and they go on to point out that in night workers the times of the maximum and minimum temperatures may be reversed. Wyatt and Marriott quote the conclusion of Teleky (writing in 1943) that this change, for most factory workers, takes place within a week, and after a change back to day work the reversion to normal is more rapid than the inversion. Teleky thought that these periods of inversion and reversion of body temperature might be associated with increased physiological strain and tentatively suggested a monthly rather than a weekly change of shifts. The Health of Munition Workers Committee also emphasized the physiological advantages of infrequent shift changes, but recognized that it might be difficult to reconcile those advantages with personal desires and social claims. This certainly seems to be the basic problem.

Wyatt and Marriott's investigation is only a preliminary study, but it brings forward valuable data and should stimulate further inquiry. They state that it was realized from the outset that conclusive evidence could be obtained only by studying the same group of workers on different shift sequences, but the facilities and conditions for such a study could not be found. As an alternative, they decided to conduct a limited inquiry in three factories

<sup>1</sup> Brit. J. Indust. Med., July, 1953.

having a weekly, a fortnightly and a monthly change of shifts respectively and so to prepare the way, if necessary, for a more extensive investigation later. The general procedure was to collect all the available records of output, accidents and absence from work which might provide reliable information on the merits and defects of night work and the frequency of shift changes. In addition a number of men in each of the three factories were interviewed to ascertain their attitudes to various aspects of the problem. The findings indicate that output on night work was slightly less than on day work, and this difference was equally noticeable whether shifts were changed weekly, fortnightly or monthly. When shifts were changed fortnightly, output on the day shift was higher in the second week than in the first week. An increase in output in successive weeks of the day shift was also noticeable when shifts were changed every month. Although most of the men produced more on the day shift than on the night shift, some (about one-third) worked just as well as or even better when on the night shift. The investigation into accident rates produced evidence that was much too inconclusive to warrant comment at this stage. The findings in relation to absence from work are rather what might be expected. Wyatt and Marriott state that although factory records are likely to show more absence among those on day work than those on night work, mainly because of the employment on day work of men who are unfit for night work, there was little difference when comparisons were limited to the same men employed on day and night work in alternate periods. However, when shifts were changed every two weeks, absence among those on the night shift was higher in the second week than in the first week of the fortnight; among those on the day shift the opposite tendency was noticeable. When shifts were changed every four weeks, the amount of absence in successive weeks also tended to increase on the night shift and to decrease on the day shift.

The interviews with the men produced some interesting material, which warrants careful consideration. It was found that almost all the men preferred day work to night work mainly because it was believed to be better for health, output and social life. The attitude to the frequency of shift changes was determined more by custom and habit than by the intrinsic merits or defects of weekly, fortnightly and monthly changes of shifts. On the matter of fatigue it is difficult to reach conclusions, but inquiries revealed that feelings of fatigue, both during and after work, were more widespread and severe on night work than on day work. Questions about meals brought some quite striking results. Most of the men said that night work caused a loss of appetite and upset digestion. After changing to night work 27% of the men took from one to three days to settle down to the new meal times, 12% took from four to six days, and 23% needed longer. A fairly large proportion (43%) took patent medicines in an attempt to counteract stomach disorders, and 33% took aspirin or similar tablets fairly frequently. Curiously enough, changes in sleeping times seemed, on the whole, to be less disturbing than changes in meal times. However, 42% of night workers claimed that they were unable to get enough sound sleep during the day, 37% had less than six hours of sleep, and 75% had less than eight hours.

Wyatt and Marriott state that the survey disclosed considerable individual differences in susceptibility to the effects of night work and shift changes. While some experienced only mild discomfort and worked just as well on the night shift as on the day shift, others were more upset by night work. It is important to remember that the men included in this inquiry were long-service workers hardened by experience and represented a selective group. However, the findings show that some men were still unable to adapt themselves to night work and were obviously unsuitable for work on a two-shift system. In general, the results suggest that more attention should be given to the selection of men for night work and to the closer medical supervision of those selected.

With regard to the question of whether shifts should be changed weekly, fortnightly or monthly, Wyatt and Marriott found the evidence inconclusive, as it had been

in previous investigations. They state that while there can be little doubt that, for most workers, the change from day to night work had unfavourable effects on sleep and digestion, it is almost equally certain that these effects had largely disappeared by the end of the first week after the change. This evidence in support of less frequent shift changes was, however, neutralized to some extent by the week-end break, when most workers reverted to normal habits of life. Further, the findings of this and earlier inquiries on absenteeism and output do not support the physiological evidence in favour of less frequent shift changes. Neither does it accord with the general dislike of night work and its interference with social and family life. On the whole, according to Wyatt and Marriott, the balance of available evidence suggests that, so long as night work is necessary, a fortnightly change of shifts would be the most effective compromise from the standpoint of health, efficiency and personal satisfaction, but further investigation is necessary before definite conclusions can be established. The only real solution to the problem, they assert, is the abolition of night work except in times of emergency and in certain continuous processes. It is certainly unpopular and, in the long run, detrimental to health, efficiency and the enjoyment of life. Wyatt and Marriott point out that in every group of workers, some breakdown in health occurs after a few weeks, months or years of night work; these are the obvious casualties, but it is reasonable to suppose that almost all workers are adversely affected in some degree and brought nearer to the point when the effects can no longer be ignored.

It would seem that the whole question needs a great deal more attention, and conclusions applicable to Australian conditions can be drawn only from investigations carried out in Australia, though they could well follow the lines suggested by Wyatt and Marriott. Incidentally, an important and quite different aspect of the whole subject, on which little light is thrown by reported investigations so far carried out, is that of women and non-manual workers on night shifts. In particular, an investigation of the effects of night work on hospital staffs is long overdue.

#### ORALLY ADMINISTERED FAT PREPARATIONS.

ONE of the factors in the treatment of sick people which have been receiving increased attention in recent years is the supplying of an adequate caloric intake. The sick person often loses weight because of inability to consume a diet of sufficiently high caloric content with deleterious effects on his recovery. Because the patient cannot consume large amounts of ordinary foodstuffs, attempts have been made to prepare mixtures which have a high caloric value in a relatively small volume. For this reason attention has been directed of late to the elaboration of formulae of various sorts in which fat, because of its high caloric value (9.3 Calories per gramme), has received especial attention. In the May-June issue of the *Journal of Clinical Nutrition* A. Grollman discusses the use of orally administered fat preparations in medicine. The superiority of fat over other foodstuffs, because of its high caloric equivalence, has long been known. The sparing action of carbohydrate on protein catabolism has also been recognized. The combination of fat and carbohydrate gives a unique combination which furnishes an easily assimilable source of Calories, represses endogenous protein catabolism, and induces the optimal efficiency in the utilization of administered protein. Because of its effects on gastric peristalsis and emptying of the stomach, fat, when given as a supplementary feeding, should be administered not with meals but preferably between meals and in the evening. Cream has long been used, but artificial mixtures have been prepared which are better. Grollman discusses mainly the use of commercial fat-carbohydrate emulsions. These contain 40% to 50% of vegetable oil (peanut, coconut) and 10% of glucose in water, to which is added an emulsifying agent, an antioxidant and a preservative. The fat is reduced to very

small particles ( $1\mu$  or less) and this removes the nauseating "fatty" taste of the oil. Such emulsions are tolerated even in relatively large doses. Grollman found that many patients tolerated readily 250 mls in addition to their usual diet, this giving about 1000 Calories per day. The fat was well assimilated, and there were only insignificant increases in the faecal fat content. The emulsions may be administered in various ways. They may be given undiluted in doses varying from 15 to 120 mls at intervals of several hours. They mix well with water, milk or fruit juices. One of the first applications for the use of fat-carbohydrate emulsions has been in the management of patients suffering from acute renal failure. The emulsions given with a sufficient amount of glucose in water, administered orally or intravenously, furnish the caloric and water requirements of the patient. The emulsions have given satisfactory results with underweight patients. They have been useful in illnesses characterized by anorexia with increased protein catabolism and negative nitrogen balance. This has been particularly the case with severely burned patients. In tuberculous patients weight loss was reduced.

#### THE AMPLITUDE OF PRONATION AND SUPINATION.

It has been said that man was made with arms and legs in pairs for the benefit of orthopaedic surgeons. No doubt this presumes too much, but at least all clinicians will agree that the most valuable way of assessing degrees of abnormality in one limb is by comparison with the other normal limb. This essentially practical point is brought home by the findings in a study by H. D. Darcus and Nancy Salter<sup>1</sup> that might quite reasonably have been regarded as mainly academic. The study is part of an investigation aimed at determining accurately the amplitude of pronation and supination of the hand and the variations that occur in its measurement. Definitions of the terms pronation and supination quoted by Darcus and Salter as being generally accepted are that, with the forearm horizontal, pronation is the movement that turns the palm of the hand to face downwards and supination that which turns the palm to face upwards. The movements are mainly dependent, when the elbow is flexed, on rotation of the radius about the longitudinal axis of the forearm at the radio-ulnar joints; associated with this is a limited degree of flexion and extension at the elbow joint, as well as a certain amount of rotation at the intercarpal joints. Despite the fact that figures for the amplitude are quoted in articles and text-books, there has been no general agreement on standards of measurement and many of the figures quoted are unsatisfactory. Darcus and Salter have sought to bring some order into the situation. For their investigation they used three types of instrument, which they describe: a hand-grip arthrometer, a wrist-cuff arthrometer and Patrick's goniometer. The largest readings were obtained with the hand-grip arthrometer, which, besides recording rotation of the radio-ulnar joints, also measures supplementary movements of the hand and wrist. Intermediate values were recorded with the pendulum type of arthrometer (Patrick's goniometer), which excludes hand movements but allows rotation at the intercarpal joints. The lowest readings were recorded with the wrist-cuff arthrometer, which measures almost exclusively movements about the radio-ulnar joints. The results in the subjects studied revealed no significant association between amplitude on the one hand and age, sex or previous injury on the other. Although differences were found between the amplitudes measured on the right and left sides of the same individual, these usually did not reach a significant level. It is particularly interesting to note that wide variations occurred between readings taken successively on the same day and from day to day. Darcus and Salter state that the cause of these variations is obscure and probably depends on a number of factors, some of which are

uncontrollable. Some variations are probably due to the experimental procedure, despite efforts to avoid this. Other observers have concluded that variations were due to the fact that the movements tested were seldom normally carried out to a maximum; thus, when a maximum effort was required, the movements were not under sufficient control and might, therefore, be performed with uncertainty. Darcus and Salter's observations suggest that training is not an important cause of variation, at least in short-term experiments; but previous observations have indicated that prolonged exercise over four years increases the amplitude of movement of the wrist joint. Variations may also result from changes in the muscular activity of the antagonists, the full nature of which is at present obscure. However, Darcus and Salter consider that the most potent factors causing variation are probably psychological in origin. They point out that it is extremely difficult, if not impossible, to keep the level of motivation of a subject constant, and thus his will to do his "best" changes from time to time. The conclusion is drawn that, even if everything is done to reduce to a minimum variations due to extraneous influences, a certain degree of variability must be accepted in all measurements of maximum values in man. The presence of these variations also serves to emphasize the hazards of drawing conclusions from a single measurement of the amplitude of any movement, especially in clinical work, where such measurements may be accompanied by discomfort or some other limiting factor. The final point is that owing to the wide limits of individual variation, "normal" figures for the amplitude of pronation and supination are of only limited value. For clinical purposes, the findings of these experiments indicate that, in cases of injury to one limb, readings from the opposite limb are a more reliable yardstick than any "normal" values.

#### TESTS FOR CAPILLARY FRAGILITY.

SINCE fragility of the capillary vessels appears to be more than an assumption, and petechial lesions are a not uncommon sign in certain conditions affecting the capillary system, it would seem advisable to inquire into the validity of tests which depend upon the appearance of petechiae in the skin. The most commonly used test is carried out by applying measurable degrees of trauma to accessible areas of skin and observing the ease or otherwise with which petechiae may be produced. Mild trauma may be applied by positive pressure (as by a sphygmomanometer cuff, which is convenient, no special apparatus being needed), or by a simple device which applies negative pressure by suction. The latter has the advantage that it can be applied on areas of skin devoid of folds and not unduly hairy. This method was used in an inquiry carried out by L. E. Hines, J. Catlin and D. L. Kessler.<sup>1</sup> They point out that certain variants of these tests are made too complicated, and that the calculation of a fragility index, as some investigators advise, not only adds complexity, but assumes a mathematical exactitude which is not justified. It is doubtful if it is fair to assume that the readings of a petechial index correspond to serial degrees of fragility of the capillaries. The authors further consider that a quantitative test depending upon a count of petechiae in a given area of skin may fail to give an accurate record of the inefficiency of the capillary endothelium. They quote Wintrobe as stating that "positive" tourniquet test results may be due to damage of the endothelial cells due to infective or allergic states, to lack of enough platelets to support the capillaries under pressure, and to deficiency of intercellular cement substance, as occurs in scurvy. These conditions are, of course, distinguished by various tests which estimate the manifold factors concerned in coagulation. Further, it does not follow that hemorrhagic phenomena in the viscera will be found to be associated with the formation of petechiae on the application of local physical stress. Hines, Catlin and Kessler noted that

<sup>1</sup> J. Anat., April, 1953.

<sup>1</sup> Am. J. Med., August, 1953.

fragility tests were not mentioned specifically by Wintrobe in relation to the vascular lesions found in hypertension and diabetes; therefore they paid special attention to this group. They discarded positive pressure tests in favour of a suction apparatus, which had the further advantage that readings could be made repeatedly without confusion caused by the presence of petechiae resulting from previous experiments. The exact technique employed need not be described here, but it may be noted that, as a sequence to previous work by Hines and Parker, the number and confluence or size of the little lesions were noted, and used as a basis of a quantitative test, in which readings of one, two, three and four *plus* were made. A negative test result was one in which no hemorrhage occurred, or in which only small petechiae, less than ten in number, were noted.

Readings were made on 102 young persons with no known abnormality of the vascular system, and on 150 persons with non-vascular forms of disease, but with normal blood pressure. The chief groups studied were those with vascular disease and normal blood pressure, those with hypertension, those with diabetes with or without vascular disease, and those with myocardial infarction. The findings confirmed previous studies which had shown that a high incidence of positive test results was found in patients with various types of vascular disease, especially when associated with diabetes. They also found that a capillary fragility could be eliminated in patients with scurvy by giving large doses of ascorbic acid, and occasionally also, though inconsistently, in the subjects of vascular disease. This suggests that there may be a collagen defect in both groups, though such a deficiency has not been proved in vascular disease in general. Some speculation may be indulged in, in relation to arteriosclerotic disease. To Hines, Catlin and Kessler their studies suggest that there is some correlation between the occurrence of spontaneous bleeding from fragile capillaries in various viscera and a defect which permits the occurrence of hemorrhages from skin capillaries during tests designed to measure their fragility.

Hines, Catlin and Kessler consider that tests for capillary fragility are at the best crude, and should be performed repeatedly on different days. However, they found, as we might expect, a higher incidence of positive test results in older people, and a very high incidence among diabetics who had hypertension or other vascular disease. This corresponded with the familiar high incidence of retinal and cutaneous hemorrhages in these patients. All patients with arteriosclerotic disease, even in the absence of hypertension, showed considerable frequency of the assumed signs of capillary fragility. Perhaps a wider use of such tests might have some prognostic value; in any event, this study helps to stimulate interest in clinical research.

## SECOND ATTACKS OF TYPHOID FEVER.

SECOND ATTACKS of typhoid fever are uncommon; indeed it is often assumed that an attack of typhoid fever confers an immunity of many years, if not of lifelong duration. F. P. Gay,<sup>1</sup> in 1918, reviewed the literature and quoted estimates varying in general from 1% to 4%, but occasionally rising to 15% when the nature of the outbreak suggested a large infecting dose. Many of these estimates are, however, open to question, as they were made at a time when the diagnosis of typhoid fever could not have been confirmed bacteriologically or serologically, and typhoid must often have been confused with other continued fevers. D. E. Marmion, G. R. E. Naylor and I. O. Stewart<sup>2</sup> describe two outbreaks of typhoid fever which occurred within a period of five months in a Royal Air Force Unit in the Suez Canal Zone of Egypt. A large number of individuals were thus exposed to the risk of infection on two occasions;

several contracted typhoid twice. The station received a piped and chlorinated water supply and drew its food from sources common to many other units in the Canal Zone. The population exposed in the outbreaks had been protected by T.A.B. vaccine, usually of the alcoholized variety.

The first outbreak occurred in April and May, 1950. Of 657 men at risk 84 contracted typhoid fever; the diagnosis was confirmed bacteriologically in 69 cases, and in 15 the diagnosis was made on clinical evidence alone. The causal organism was *Salmonella typhi* of phage type J. The outbreak was insidious in character; it was considered likely that a native cook, who was found to be a heavy urinary excretor of *Salmonella typhi*, was the cause of the outbreak, because it ceased about ten days after his removal from duty. However, the organism isolated from his urine was rough and could not be phage-typed. The second outbreak occurred during July and August, 1950. Of 688 men at risk 235 contracted typhoid fever; the diagnosis was confirmed by cultural methods in 221 cases and by a rise in somatic agglutinins in seven, and in seven cases the diagnosis was made on clinical evidence alone. The causative organism was of phage type EI—a type, incidentally, that has occurred in New South Wales lately. This outbreak was explosive in character and showed two waves of incidence within four weeks. It appeared that food eaten at midday on July 12 was the cause of the primary wave of cases; two food-handlers, who were found to be excreting the organism during the incubation period before they developed the disease, were considered to be the probable source of infection of the secondary wave of cases. The outbreak ceased ten days after their removal from duty. The second outbreak proved to be both larger and more severe than the first; 11 patients contracted typhoid fever twice. Both these facts must make us revise our ideas of immunity in typhoid fever. The authors emphasize the fact that patients who had typhoid fever in the first outbreak were not allowed to return to duty until they had completed a long graduated convalescence under medical supervision. The attack rate in the first outbreak was 12.8%, while that in the second was about three times as great. Of 438 men exposed to infection twice, 200 contracted typhoid fever on one or both occasions; this is a disconcertingly high attack rate for a community whose members were nearly all "protected" by inoculation with T.A.B. vaccine. It is equally disconcerting to learn that there was no significant difference between the attack rates of those who were exposed to infection during the first outbreak but did not contract typhoid and those who joined the station between the outbreaks and had not therefore been recently exposed to the risk of infection.

The authors remark that the influence of chloramphenicol therapy upon immunity is doubtful. There is much clinical evidence from other sources that chloramphenicol interferes with the development of immunity. Most of the patients in the first outbreak were treated with chloramphenicol. Of the 11 patients who suffered two severe attacks of typhoid, six received chloramphenicol in their first attack and five did not. As these authors point out, the influence of chloramphenicol upon immunity remains *sub judice*. There is no doubt that its use shortens the course and lessens the severity of the disease; apparently there were no deaths and few serious sequelae from these two severe outbreaks of a disease that once carried a very high mortality. As to the occurrence of typhoid in an inoculated community, it must be remembered that all immunity is relative and can be broken down by a sufficiently large dose of the infective agent. These outbreaks, serious though they were, are not to be compared with the devastating ravages of typhoid fever in the days before protective inoculation was available. No one today would dream of questioning the value of T.A.B. vaccine; the lesson to be remembered is that at the best it confers a relative and not an absolute protection. We are winning the war against infectious disease, but we cannot afford to be over-confident of our knowledge; the enemy can still surprise us.

<sup>1</sup>"Typhoid Fever", New York, Macmillan.

<sup>2</sup>J. Hyg., June, 1953.

## Abstracts from Medical Literature.

### DERMATOLOGY.

#### Terramycin Therapy in Acne Vulgaris.

R. B. BARNARD AND L. R. ORENS (*New York State J. Med.*, June 15, 1952) report observations on patients continually ingesting one of the streptomycin-derived antibiotics ("mycins") in doses considerably less than those used for the treatment of infectious conditions, and of the order of magnitude of amounts given poultry, hogs and domesticated fur-bearing animals as a feed supplement. They state that these doses fail to yield any appreciable blood or systemic antibiotic level, but do, nevertheless, produce definite metabolic and therapeutic effects in the ingesting individual. These effects are found chiefly in patients with "atopic" or "adaptive" disease and may be conditioned by the antibiotic-induced change in intestinal bacterial flora, during which saccharolytic, Gram-positive forms come to predominate over the usual Gram-negative, proteolytic organisms. The dose of terramycin was individualized and consisted of sufficient amount of the base, taken once daily, to render and maintain an odourless, copious stool.

#### Chronic Leg Ulcers Associated with Blood Dyscrasias.

FRANCES PASCHER AND R. KEEN (*Arch. Dermat. & Syph.*, October, 1952) state that blood dyscrasias, particularly the congenital hemolytic anemias, are of primary importance in a consideration of the possible causes of chronic recurrent ulcers of the leg. An association of leg ulcers with sickle cell anemia is generally better appreciated than the relationship of this symptom to other forms of congenital hemolytic anemia, such as congenital hemolytic icterus (familial acholuric jaundice, spherocytic anemia) and Mediterranean disease (Cooley's anemia, thalassemia). In addition to the conditions already mentioned, Gendel lists the following: Banti's chronic hemolytic polycythemia, Gaucher's disease, pernicious anemia and chronic hemolytic polycythemia. Gendel did not include *polycythemia vera*. However, ulcerations of the lower extremities and peripheral vascular complications have been reported by others in this dyscrasia. The authors report five cases of blood dyscrasias in which the patients sought dermatological care because of chronic leg ulcers. The hematological entities represented in this group are one case of sickle cell anemia, one case of Mediterranean anemia, one case of (possibly) congenital hemolytic icterus and two cases of polycythemia. These cases are described in detail, and the importance of a consideration of blood dyscrasias in the differential diagnosis of leg ulcers is emphasized.

#### Pilonidal Sinus of the Hand.

M. WAISMAN AND R. C. OLIVETTI (*Arch. Dermat. & Syph.*, October, 1952) state that among barbers, penetration of cut hairs into the skin of the hand is a familiar occurrence. Clinically there

develops a pit or sinus between the fingers, from which protrude short, loose, easily removable hairs of different lengths, colour and texture. This sinus may become converted into an abscess, intermittently flaring up and discharging, or the sinus may communicate a short distance proximally on the interdigital web with a nodule in which inflammatory manifestations are provoked by the embedded hairs. Although any space may be affected, most of the reported lesions have occurred between the third and fourth fingers. The commonest instance of penetration of hairs occurs in beards in the form of ingrowing hairs. Hairs which accumulate between a barber's fingers may find their way into a minute depression of the skin, such as a crease or groove or abrasion. A tiny pit is produced. As more hairs are trapped, and especially with complicating infection, the opening persists and enlarges, and the track progressively elongates through the loose connective tissue of the interdigital web. In some cases a small abscess in the web is the only manifestation of the lodgement of the hairs. In other cases hairs protruding from the opening indicate the persistence of the sinus, which can intermittently discharge. A foreign body granuloma is established. A case of interdigital sinus is presented. Treatment consists of either total excision or incision and curettage of the diseased tissue.

#### Nummular Eczema.

P. CROSS (*New York State J. Med.*, September 1, 1951) states that to recognize nummular eczema one must be guided not only by the clinical appearance, but also by its typical history, clinical behaviour and therapeutic response. The eruption consists of coin-shaped patches of eczematous dermatitis in various stages of evolution. The fully developed lesion is an erythematous, somewhat edematous plaque usually studded with small vesicles, papulo-vesicular lesions or pinhead-sized crusts. The diameter may vary from that of a dime to that of the palm. When a patch undergoes involution, the erythema and edema subside, while discrete papules and vesicles remain throughout the area. At times central healing is observed. Recurrences after temporary healing reappear at the previously affected areas and may develop into solid plaques or consist of discrete papules and vesicles in the area previously involved. Persistent patches may become lichenified without losing the tendency to vesicle formation. Oozing, when it occurs, is from small pin points. Other lesions which occur in nummular eczema are rhagadiform eczema, winter eczema and bath eczema. The typical distribution is on the extended surface of the extremities, including the dorsum of the hands and feet. The disease is commoner in adults and older people; aging of the skin seems to be a contributing factor. The whole skin surface should be examined. Asteatosis or xerosis, with ichthyosiform or fine bran-like scaling over the exterior surfaces, and dryness, scaling and lichen pilaris over the elbows, knees and buttocks are some of the criteria to be looked for. Faulty bathing habits, occupational use of soaps, cleansers and alkalis, and poor dietary habits pointing to vitamin deficiencies should be looked for. In the differential diagnosis,

atopic dermatitis should be considered, as well as contact dermatitis, dermatophytosis or dermatophytid of the hand and so-called infectious eczematoid dermatitis. The prevalence of nummular eczema in the cold season or in a cold climate, a high sensitivity to soaps and alkalis, and evidence of asteatosis of the skin are essential features of the disease. The eczematous lesions are not the result of contact, food, drug or bacterial allergy manifestations, but are due to a peculiar skin reactivity caused by metabolic disturbance of the skin. In therapy, the author advises the avoidance of soaps, alkalis and all other agents which tend to increase the pH of the skin, protection of the skin against cold, wind, friction and infection, and treatment with coal tar. Dietary therapy to correct metabolic disturbance of the skin consists of administration of vitamin A and a diet of high protein, high vitamin and moderate fat content.

#### Persistence of Skin Sensitivity.

J. K. MORGAN (*Brit. J. Dermat.*, March, 1953) states that clinical observation confirms that cessation of contact with the offending agent will usually result in disappearance of the eczematous reaction produced, although there may be some delay. However, there is less general agreement on how long a person retains a specific sensitivity, once acquired, and remains liable to reproduce the eczematous reaction if brought in contact with the offending agent once more. The author was presented with the opportunity of studying a group of persons who were known at one time to have been sensitive to nickel and to have given positive results in patch tests with that substance. It was thought that it would be of value if those patients were followed up and their sensitivity to nickel was reassessed after an interval of time. The group selected contained all those patients who had given positive results in patch tests with nickel sulphate solution in the department during 1940 to 1949 inclusive; it comprised 58 subjects, of whom 53 were women and five were men. Apart from the primary site, in many cases, once the condition was established, there were additional eczematous reactions at other sites where nickel was in contact with the skin. No less than 57% of the patients had on their original visit had a secondary eczematous spread to sites other than those in contact with nickel, particularly the elbow flexures, face and neck. Thirty-one patients had a persisting sensitivity, confirmed by the presence of contact eczema with continued exposure, or freedom if contact was avoided. Twenty-three patients gave negative results to patch testing. The loss of sensitivity was generalized and could not be constantly related either to continued contact, with possible "hardening", or to avoidance of further contact. Eighteen of these patients continued to have eczema, although no longer "nickel-positive". It is suggested that in a proportion of these patients, the specific sensitivity to nickel, which in nine instances did not last more than eighteen months, could be regarded as merely a transitory phase in the course of a series of eczematous reactions, many of them non-specific in character. The prognosis of patients with initial positive responses to patch tests with nickel in this series was therefore complex, but

appeared in a certain number to be independent of the continuance or otherwise of contact with nickel. The author states that as the majority of those who became insensitive to nickel in due course continued to suffer from eczema, it seems that the constitutional background of the individual is often of much greater significance with regard to prognosis than the initial specific external agent.

#### Acne Neonatorum.

F. L. GIKNIS, W. K. HALL AND M. M. TOLMAN (*Arch. Dermat. & Syph.*, December, 1952) review previously reported cases of *acne neonatorum* and conclude that the disease favours the male sex; in 12 reported cases the patients were boys, and in only five were they girls. Comedones were present in all cases, and papules and pustules in most cases. In one instance each, cystic lesions and deep-seated nodules were present. The cheeks were usually involved, and occasionally were the only sites involved. The chin and forehead were the next commonest sites of involvement. Sometimes erythema, dryness, papules or milia were noticed very shortly after birth, with comedones and secondary lesions appearing within weeks to months thereafter. In most cases, typical lesions were noted by the third month. In those cases followed until remission occurred, the duration was usually less than eight months. Therapy was conservative. The authors state that in earlier reports bacterial infection was considered the prime aetiological factor, but at present a hormonal factor is frequently considered. In the older literature, the condition known as "grouped comedones" was reported. In the authors' case, many comedones, papules and pustules were present on the cheeks, chin and forehead. There was moderate *seborrhoea capitis*. No evidence of endocrinopathy was present, and there was no reason to suspect *adenoma sebaceum*. Treatment consisted of the application of mild drying shake lotions. Five months after the onset of the eruption, the pustules and papules had subsided. The authors are of the opinion that *acne neonatorum* is *acne vulgaris* occurring in infants.

#### UROLOGY.

##### Diverticulum of the Male Urethra.

E. N. KHOURY (*J. Urol.*, February, 1953) states that diverticulum of the male urethra is rare, for up to 1951 only 197 cases had been reported, and the grand total up to the end of 1952 was 235, including two personal cases reported in this paper. Diverticula of the female urethra, on the contrary, are relatively common. This is not surprising when one considers the poor anatomical support available to the floor of the female canal. Diverticula in the male may be congenital or traumatic. Congenital sacs may appear clinically only after the influence of obstruction, of hormones (estrogens) or of nerve injury has been felt, but they may be clinically apparent before the introduction of any of the above three factors. Traumatic diverticula may be from (a) mechanical trauma,

(b) chemical trauma (caustics *et cetera*) or (c) inflammatory trauma (as in periurethral abscess proximal to a stricture). The most constant sign of a diverticulum is the development of a mid-line mass which is fluctuant and empties on pressure. The mass enlarges during micturition and may cause delayed dribbling. Final diagnosis is made by panendoscopy and cystourethrography. Complete excision is the ideal method of treatment.

##### Current Treatment of Prostatic Carcinoma.

H. BRENDLER (*J. Urol.*, October, 1952) states that much progress has been made in the palliative treatment of prostatic carcinoma, but very few actual cures of the disease have so far been demonstrated. Largely as a result of the original contributions of Charles Huggins, most prostatic cancer patients live more comfortably than they did in the pre-endocrine era, and it is possible that some of them live longer. However, the tendency to draw specious conclusions regarding true cure from analysis of any five-year survival series is to be deplored. On the other hand, though the natural course of the untreated disease is a slow one, it has been shown, by the pooled statistics survey by Nesbit and Baum in 1950, that the results of anti-androgenic attack (including bilateral orchidectomy) gives longer survival as well as greater comfort. A difficult problem is that of late relapse. Despite apparent control of the disease for several years, the patient, in most cases, suffers inevitable recurrence or reactivation of the malignant process. A synthetic oestrogen, tri-p-anisylchloroethylene ("TACE"), is being tried with some apparent success in such cases. The possibility that increased amounts of adrenal androgens are responsible for the relapse has led to the use of cortisone in an effort to cause inhibition of adrenal cortical activity. Bilateral adrenalectomy, though a drastic procedure, is also being tried. As regards degree of malignancy, it is now apparent that morphological classifications are not often sure criteria of neoplastic behaviour. A need exists for methods by which the biological potential, or inherent malignancy of individual growths may be determined. Elevation of serum acid phosphatase level in patients without demonstrable metastases is indicative of a worsened prognosis. This conclusion was reached by Nesbit and Baum, and the same workers have shown, in patients with metastases, that though the serum acid phosphatase level is usually raised, a normal reading is not a sign of low bodily resistance to the disease, and hence does not mean a poor prognosis.

##### Retrocaval Ureter.

P. R. LEBERMAN, H. H. ZINSSER AND D. F. MILAM (*J. Urol.*, October, 1952) state that retrocaval ureter is an interesting anomaly which is rapidly ceasing to be a urological oddity. The case they report is the forty-fifth in the literature. Their patient, a man of twenty-three years, had pain in the right flank, and excretion urography showed a large hydronephrosis with dilatation of the upper part of the ureter. The actual diagnosis of retrocaval ureter, with obstruction at the place of crossing, was made before

operation, for the retrograde pyeloureterogram made this clear. The uppermost (dilated) part of the duct described an S-shaped curve, while the channel below this deviated medially, lying over the vertebral bodies in the lower part of the lumbar region. At operation the ureter was freed as it passed behind the *vena cava*. The dilated ureter was divided only four centimetres below the uretero-pelvic junction, and the lower segment was removed from behind the *vena cava*. The division was made obliquely, and the freed lower segment was anastomosed to the upper one by "00000" chromicized catgut on an atraumatic needle. A 10F soft ureteric catheter was left in as a ureteric splint for fifteen days, while a nephrostomy drain was retained for twenty-one days. The result was good, and a remote check at the end of six months showed that the renal pelvis was reduced almost to normal size.

##### Congenital Neurogenic Vesical Dysfunction.

C. L. PRINCE AND P. L. SCARDINO (*J. Urol.*, April, 1953) state that myelodysplasia and *spina bifida* are often the cause of grave, even fatal, urinary tract disorders in children. Apart from the urinary tract disease, other findings are rectal incontinence, severe motor and sensory changes in the lower extremities, club feet and hydrocephalus. The high mortality and short life expectancy are chiefly due to the urinary tract complications. The authors have followed two severe cases of this type in little boys over a period of several years. These have been managed conservatively, without surgical operations of any type, and the results have been gratifying. Infection and residual urine have been eliminated in both instances. In both instances there has been a surprising improvement in upper urinary tract dilatation, with restoration of renal function to normal. The authors state that the methods of management usually recommended are permanent suprapubic cystostomy, endoscopic resection of the vesical neck and, less often, bilateral nephrostomy. Cystostomy and nephrostomy are, however, inconvenient and messy, as well as difficult to manage in young children; infection is inevitable and stone-formation a frequent complication. Endoscopic resection has been far from satisfactory in achieving the desired end results. The authors were determined to manage the cases of the two little boys conservatively if possible, and did this by the method of regular suprapubic pressure. Very little pressure was required to empty the bladder with a good flow, this indicating little or no bladder neck obstruction. The authors state that if panendoscopy reveals bladder neck obstruction, endoscopic resection should be performed; otherwise the pressure method is best. There should be a rigid routine of emptying the bladder by manual suprapubic pressure, and proper chemotherapy to control infection. One of the two children has gained good urinary control, and both have learned to empty the bladder without assistance. Usually the mother can be taught to empty the child's bladder by manual pressure every two hours in the day and every four hours at night.

## Special Articles for the Clinician.

(CONTRIBUTED BY REQUEST.)

LXXXVI.

### PARALYSIS AGITANS.

PARKINSON'S SYNDROME was first described clinically by James Parkinson in 1817. It was not until nearly a century later that Ramsay Hunt, Jacob and later Vogts described degenerative changes in the cells of the *globus pallidus* of the *corpus striatum*, and it came to be recognized that Parkinson's disease or *paralysis agitans* was primarily a disease of the extrapyramidal motor system.

In complete lesions of the pyramidal motor tract certain movements can be carried out by the paralysed muscles under the influence of appropriate stimulus. The lower limb will tend to withdraw when the sole of the foot is stimulated, the patient can smile and yawn though unable to produce voluntary movements of the facial muscles. These movements of a more primitive type are the function of the older paleomotor system, which has at least important relay stations in the *corpus striatum*. Normally there is a complete fusion between voluntary and automatic movements, and one of the early symptoms of loss of function of the striatal system is slowness of movement due to the lessening of the automatic component of muscle movement. This slowness of movement or bradykinesia is commonly observed in the young subject with post-encephalitic early Parkinson's syndrome, and is quite independent of the rigidity which appears as the disease progresses. Hughlings Jackson pointed out many years ago that destructive lesions of the central nervous system produced not only negative symptoms due to loss of function, but positive and often more devastating symptoms due to uninhibited activity of other parts of the normally functioning nervous system. Loss of automatic swinging movements of the arm in walking, and loss of facial movements of expression, are negative symptoms due to paleomotor or striatal degeneration. Tremor and rigidity come under the heading of release phenomena.

Certain other degenerative diseases of the *corpus striatum* may bring about tremors and forced movements—not characteristic of Parkinson's syndrome, though there may be some superficial resemblance between them. There are, however, pathological conditions in which there are widely different aetiological factors. Such conditions, which may produce the syndrome with perhaps varying side effects, are as follows: (i) Primary senescence of the large cells of the *globus pallidus*, the so-called idiopathic *paralysis agitans*. (ii) Arteriosclerotic changes in these cells, often accompanied by similar changes in other parts of the central nervous system. (iii) The sequelae of epidemic encephalitis, in which the weight of pathological changes is seen in the *substantia nigra*, which has close connexions with the motor cells of the *corpus striatum*. (iv) Rarer causative conditions, such as syphilis, trauma, hemorrhage into the *corpus striatum* and tumours.

#### Symptoms and Course of the Disease.

As there has not been an epidemic of *encephalitis lethargica* since the 1920's, it is somewhat rare to see young and juvenile sufferers from Parkinson's syndrome, with its insidious onset and tragically inexorable, and sometimes rapid, march of events crippling a young and useful life. The more common form is that seen in advancing age—the true *paralysis agitans*, either the primary senescent or the arteriosclerotic type. The disease has an insidious onset in about the middle fifties, and it may be many years before there is any degree of disablement. An early diagnosis may save the patient unnecessary investigation, and enable the physician to prolong the patient's period of useful life until he reaches an advanced age.

The description of the signs and symptoms of Parkinson's syndrome will be confined to those appearing early in the disease, when there may be some difficulty in determining the diagnosis. The march of events will sooner or later unfold, the typical picture needing little descriptive elaboration.

The onset may be unilateral, though it is usually bilateral, one side in the early stage being more affected than the other. The patient complains of a sense of weakness and slowness in movement in an upper or lower limb. There may be little to find on objective examination, though a

suspicion of a tremor of the hand at rest may be noted. The text-book pin-rolling type of tremor does not appear until the more advanced stage is reached. The tremor at this stage may be noted only at rest, and on objective examination is likely to disappear. Close observation of the patient when walking may reveal a slight absence of the swinging action of the affected arm or an almost imperceptible dragging of one leg. The unilateral distribution of symptoms may persist for months and even years before the opposite side becomes affected.

The earliest manifestation of Parkinsonian facies may be evidenced by a faintly staring appearance, owing to the involvement of the automatic blinking movement of the eyelids. When this is accompanied by tremor, the suspicion of early Graves's disease may arise. Gradually loss of emotional facial expression, together with a degree of loss of expressional vocal cadence, may become evident. Any one of these early symptoms may appear individually, though in retrospect one will realize that there has been close proximity, however slight, to the combination of such symptoms, and it is curious how suddenly a perception of the whole clinical picture will present itself.

An early objective sign may be observed in slight so-called cogwheel rigidity of the affected limb. This rigidity can be felt only when the patient is asked to relax the limb as much as he can. Writing becomes smaller and more difficult until micrographia results. As the disease advances the typical posture and gait make their appearance.

In post-encephalitic Parkinsonism the march of events may be very much more rapid, and advanced symptoms may appear within a year of the onset. Salivation may appear as an early symptom, and may be most distressing. Loss of convergence of the eyes may also appear early, and the oculogyric crisis, in which the eyes look up and cannot be brought down to the normal level for perhaps some hours, is a later symptom. These latter symptoms are not seen in other forms of Parkinson's disease.

#### Differential Diagnosis.

In the early stages the tremor may be mistaken for that of other neurological conditions, such as disseminated sclerosis, Huntington's chorea, and lenticular degeneration. The chief characteristic of Parkinson's tremor is that it appears at its maximum when the patient is at rest, and may temporarily be controlled. The tremor of senility, which may and often does occur without any evidence of mental degeneration, is more constant, and is present without any of the accompanying Parkinsonian symptoms.

From the psychiatric viewpoint functional tremor may be difficult to exclude, especially in the presence of weakness of a limb and in the absence of other signs and symptoms. Many early cases of post-encephalitic Parkinsonism in young people have been confidently labelled as hysteria, and treatment for that condition has been given until the onset of the more obvious symptoms. The facies may give the appearance of the melancholic. The bradykinesia, and the tendency that some patients have to immobilize a limb in a fixed posture, may give rise to doubt whether one is confronted with a case of catatonic schizophrenia.

*Paralysis agitans* does not *per se* produce mental degeneration. If arteriosclerosis is the pathological basis of the disease, similar changes may occur in other parts of the brain, producing intellectual degeneration, confusion and delusional states. The patient is often depressed owing to his condition, although an independent involutional depressive state may be incidental to the accompanying Parkinson's disease, and is amenable to treatment.

#### Treatment.

The treatment of Parkinson's disease falls under two headings, first the management of the individual patient, and secondly drug therapy. As the disease usually runs a long course, extending often over a number of years, long-range plans have to be adopted to cater for the patient's mode of life.

The diagnosis is often made before the patient suffers from any particular discomfort, when he is leading a normally active life. In the early stages it is usually the tremor of the hands, often unilateral, that draws the patient's attention to his condition. The Parkinsonian facies, the muscle rigidity, the typical gait and posture, though faintly perceptible to the observer, are not of great moment to the patient until the disease becomes well established. As the tremor develops the patient often becomes self-conscious and sensitive, feeling that it is being noticed and trying to hide it—an attempt which only makes the tremor more

noticeable, and so increases the embarrassment of the patient. It is in this early stage that the physician has to decide how much he is going to tell the patient of the true nature of the disease; this depends very much upon the personality of the patient. On the whole, it is well to adopt a reassuring attitude, and to point out that although the tremor is not likely to lessen, the patient can look forward to years of useful life, and that if he does not try to hide the tremor no one is likely to take notice of it; a little mild sedation may help to allay the anxiety. It is doubtful whether at this stage anti-Parkinsonian drugs are indicated, because of their toxicity and of the tolerance that may be exhibited towards these drugs. As a rule a philosophical attitude is taken, and a sense of relief and even mild euphoria are expressed when the patient is told that normal working life is to be maintained. Later on a true depressive state of the involutional type may make its appearance, necessitating special treatment—which, by the way, in no way alters the course of the disease, but may produce definite relief of the depressive symptoms. As the disease progresses there seems to be a process of adaptation on the part of the patient; any relief that can be given is eagerly accepted, and there is a degree of suggestibility which may present difficulties in evaluating the effect of a drug, especially if it is a new one to the patient. There is no doubt that an emotional stimulus will temporarily allow the pyramidal motor system full play.

I recollect a young man suffering from moderately advanced post-encephalitic Parkinson's syndrome who went to a wedding party, and under the influence of a modicum of alcohol, and the company of a good-looking young woman, danced the night, and according to my informant showed little evidence of his illness during this period, although he had lapsed into his normal Parkinsonian state when I saw him a few days later.

It is this variability that may cause a diagnosis of hysteria to be made in early encephalitic *paralysis agitans* in a young patient.

In the advanced stages of *paralysis agitans* mental symptoms may appear; these symptoms may be due to arteriosclerotic changes in the brain, and may take the form of dementia often accompanied by delusions. The difficulty in managing these patients is increased by their increasing immobility, though even in these patients acts of violence under the emotional influence of a delusional content will astonish the nursing staff, which has hitherto regarded the patient as bedridden and immobile.

As the disease advances, rigidity becomes increasingly troublesome and disabling to the patient. The characteristic gait, posture and tremors are proportionately increased, and the necessity for using some drug that may alleviate some of these symptoms becomes essential. Treatment of *paralysis agitans* in the aged is a geriatric problem.

Once treatment by drugs has been commenced, it has to be continued indefinitely. Drugs of the alkaloid group give relief, and if they are discontinued the patient suffers greatly. For this reason it is wise to give small maintenance doses for as long as possible. All drugs, whether of the alkaloid or the more recent synthetic group, produce side effects, some of which are unpleasant and produce toxic symptoms. The main object of such treatment is to reduce the rigidity, and if possible the tremor, so that the patient may remain ambulatory and as comfortable as possible for as long as possible. The belladonna, atropine and hyoscine group of drugs act mainly by inhibiting certain striatal reflex arcs, as the rigidity results from the spread of extrapyramidal reflexes from the damaged *corpus striatum*. Hyoscine hydrobromide, one one-hundredth of a grain by mouth two or three times daily, gives relief of the rigidity, and in post-encephalitic Parkinsonism reduces the profuse salivation which is so distressing to the patient, and which may appear early in the course of the disease. This salivation does not make its appearance in the early stages of *paralysis agitans* of other aetiology. As the alkaloids produce undesirable side effects after prolonged usage, there have of recent years appeared a number of synthetic drugs whose relative values increase as the toxic effects are diminished. There appears to be some personal idiosyncrasy which has to be discovered by trial and error, in order to find out which of these drugs gives the greatest relief with the least possible toxic effect on the individual patient. It must be remembered that the psychological effect of a "new treatment" is likely to produce a feeling of fictitious well-being, so that it may take some time to evaluate the true therapeutic value of a particular drug. There is an imposing list of drugs used; all have their adherents, and no doubt each has its value in certain cases. The list consists of "Artane",

"Diparcol", "Benadryl", "Lysivane", "Myanesin", dihydro- $\beta$ -erythroidine, "Amphetamine", MK-02 and "Panparnit".

Raffle (1952), in a brief review of his own experiences with some of these synthetic drugs, considers that "Artane" by its stimulating effect upon the damaged extrapyramidal system produces the most satisfactory results. Doses of 10 to 15 milligrammes per day, gradually increased to 20 milligrammes, increased the patient's sense of well-being and lessened the rigidity and tremors. There were very few unpleasant side effects.

"Amphetamine", given in doses of 10 milligrammes thrice daily, is an antihypnotic and increases the patient's energy, but does not give the muscle relaxation attributed to "Artane".

"Diparcol" belongs to the antihistamine group of drugs, and gives relief of muscle rigidity, so increasing the patient's mobility, but produces unpleasant toxic effects after prolonged usage. Pilcher (1950) describes two cases of agranulocytosis following prolonged "Diparcol" treatment. The dosage given was 0.05 grain daily, increasing daily up to 2.0 grains. After two weeks the dosage is decreased until the toxic effects are at a minimum. Lethargy, dizziness and malaise are sometimes noted. Reid (1950) found that these side effects were sometimes controlled by amphetamine sulphate or caffeine. He reports good results from "Diparcol" therapy in 27 out of 37 cases; one was an advanced case of hemiplegic distribution, and the patient's gait returned to approximately normal.

"Lysivane" also belongs to the antihistamine group. Given in doses of 0.05 grain increasing to 0.2 grain every six hours, it produced satisfactory results in a number of cases. Drowsiness, nausea and vomiting appeared after the end of the first week; but these effects gradually subsided as the treatment continued. Gillhespy (1951) reports improvement in 77% of 150 patients treated. Garai (1951) treated 51 patients with "Artane" and 43 with "Lysivane" (24 of these patients were receiving both "Lysivane" and "Artane"). He divided his cases into four groups: idiopathic, arteriosclerotic, post-encephalitic and miscellaneous. He found that patients in the post-encephalitic group could tolerate from 50 up to 100 milligrammes of "Artane" per day satisfactorily; in the other group a dose of 20 milligrammes per day was about the average. He found benefit with both drugs, though the side effects of "Lysivane" were in some cases so severe that treatment had to be discontinued. These effects were drowsiness, confusion, giddiness, blurred vision, nausea and vomiting. On the whole "Artane" was less toxic and controlled the rigidity and even the tremor more satisfactorily.

Shapiro and Baker (1950) treated 24 patients with dihydro- $\beta$ -erythroidine. This is a curare-like substance which is effective only if given in conjunction with "Rabellon" or hyoscine. Gastro-intestinal symptoms occurred in a few cases, though doses of up to 400 milligrammes per day in most cases were found to be non-toxic; 50 milligrammes four times a day was the usually effective dosage.

Doshay, Constable and Fromer (1952) have used a component MK-02. This consists of the tropine portion of the atropine molecule, and the benzohydryl portion of the "Benadryl" molecule. This substance has atropine and antihistamine properties, and is said to be non-toxic. Patients with post-encephalitic Parkinsonism could tolerate two to five milligrammes per day. Other forms of Parkinson's disease reacted favourably to doses of 0.5 to 1.0 milligramme twice a day. Listlessness and depression occurred in some cases after several months, and "Artane" was added in these cases because of its stimulating effect. In large doses MK-02 acted as a very efficient muscle relaxant.

"Kemadrine", a still more recent drug closely allied to "Artane", has more recently come into the market, and is put up by Burroughs Wellcome and Company. Montuschi (1952) has used this drug with some success.

The use of "Panparnit" (caramiphen hydrochloride) in the treatment of diseases of the basal ganglia was described by Sciarra, Carter and Merritt (1949). Doses of 12.5 milligrammes three times daily increasing up to 800 milligrammes per day were given. Dizziness, anorexia, blurred vision and diplopia occurred in a large percentage of cases, and although the condition of some patients appeared to improve, the report on the whole regarding treatment of Parkinson's syndrome was not encouraging.

Vollmer (1951) is not impressed with "Artane" therapy, and considers that massive doses of atropine and "Rabellon" (also an alkaloid) have on the whole stood the test of time in the treatment of *paralysis agitans* over a long period.

"Myanesin" is a curare-like drug which, when given intravenously, will produce muscle relaxation and will diminish

the tremor of *paralysis agitans*. It does not seem to be of great practical value as a long-range therapeutic agent.

This very brief summary of some of the more recent synthetic drugs used in the treatment of Parkinson's syndrome does not show that there is any very great advance over the former use of the alkaloids such as hyoscyne and atropine. As Parkinson's disease progresses, so do the critical faculties of the patient recede, and the patient becomes increasingly suggestible. There is little doubt that all these drugs do produce some relaxation of rigidity, and if treatment is discontinued the rigidity and general discomfort are greatly increased.

The question of tolerance to any one drug is of importance in assessing its value over a long period. It would appear that "Artane" is a drug that is well tolerated in large doses, though this is subject to individual variation. It is undoubtedly wise for the physician who is treating a patient with advanced Parkinson's disease over a long period to vary the treatment from time to time.

Suggestion certainly does play its part in almost every new therapy presented to the patient, and provided patience, care, judgement and enthusiasm, on the part of the physician, can be maintained, the patient will show some response, and will be ever grateful.

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#### References.

- DOSHAY, L. J., CONSTABLE, K., and FROMER, S. (1952), "Preliminary Study of a New Anti-Parkinson Agent", *Neurology*, 2: 233.
- GARAI, O. (1951), "Lysivane and Artane in the Treatment of Parkinsonism", *Lancet*, 1: 429.
- GILLHESPY, R. O. (1951), "Lysivane" in the Treatment of Parkinsonism", *Brit. M. J.*, 2: 301.
- MONTUSCHI, E., PHILLIPS, J., PRESCOTT, F., and GREEN, A. F. (1952), "Kemadrin in Postencephalitic Parkinsonism", *Lancet*, 1: 582.
- PILCHER, R. B. (1950), "Agranulocytosis following Treatment of Parkinson's Syndrome with 'Diparcol' (Diethyl-Amino-Ethyl-Phenothiazine): A Report of Two Cases", *M. J. AUSTRALIA*, 2: 295.
- RAFFLE, R. B. (1952), "Experiences with the Newer Drugs in Parkinsonism", *Practitioner*, 168: 62.
- REID, W. L. (1950), "Treatment of the Tremor-Rigidity Syndrome (Parkinson's Syndrome) with 'Diparcol'", *M. J. AUSTRALIA*, 1: 465.
- SCIARRA, D., CARTER, S., and MERRITT, H. H. (1949), "Caramiphen Hydrochloride (Panparit) in the Treatment of Diseases of the Basal Ganglion", *J.A.M.A.*, 141: 1226.
- SHAPIRO, S., and BAKER, A. B. (1950), "Treatment of Paralysis Agitans with Dihydro-beta-erythroidine", *Am. J. Med.*, 8: 153.
- VOLLMER, H. (1951), "Pitfalls in Evaluating Drug Therapy of Parkinsonism: Comparative Effects of Rabellon and Artane", *New York State J. Med.*, 51: 1933.

## British Medical Association News.

### SCIENTIFIC.

A MEETING of the New South Wales Branch of the British Medical Association was held at the Royal Prince Alfred Hospital, Camperdown, on May 21, 1953. The meeting took the form of a series of clinical demonstrations by members of the medical and surgical staffs of the hospital. Part of this report appeared in the issue of October 31, 1953.

#### Juvenile Diabetes and Myxœdema.

DR. R. B. BLACKET and DR. K. S. HARRISON showed a twelve-year-old girl who had first come to the diabetic clinic in September, 1952, with typical symptoms of diabetes. She weighed six stone two pounds and her fasting blood sugar value was 275 milligrammes *per centum*. Two hours after ingestion of 50 grammes of glucose it was 400 milligrammes *per centum*. She was treated with insulin, 12 units of soluble and 20 units of protamine zinc each morning, and a 2000 Calorie diet. When examined in February, 1953, she weighed seven stone eleven pounds, and she had had no glycosuria for three months. She had become lethargic and apathetic. On examination she presented most of the features of myxœdema—dry skin and hair, non-pitting œdema, cold extremities and bradycardia. Her basal metabolic rate was -40% of normal and her serum cholesterol value 570 milligrammes *per centum*. Her fasting blood sugar value was 110 milligrammes *per centum*, and it rose

to 280 milligrammes *per centum* two hours after ingestion of 50 grammes of glucose. Her electrocardiogram showed right bundle branch block, but there was no clinical abnormality of the heart. Insulin administration was stopped, and no glucose was found in the urine. She was given increasing doses of thyroid extract and slowly began to lose weight and regain her normal appearance and vitality. In early April she weighed six stone nine pounds and glycosuria had recurred, but there was still no significant change in her glucose tolerance. Her basal metabolic rate was now -12% of normal, and her serum cholesterol value was 200 milligrammes *per centum*. At the time of the meeting she was again taking the same diet and insulin as in the previous September and was feeling well. Her condition was regarded as one of juvenile diabetes and myxœdema with an incidental right bundle branch block.

#### Atypical Trigeminal Neuralgia.

DR. R. READER showed a man, aged forty-three years, who had suffered paroxysmal left-sided headaches since 1944. The attacks lasted for one to three hours and occurred at intervals varying from one day to several weeks. They affected the left eye and the left frontal and temporal region and sometimes spread to the occipital region. The pain was constant, "boring" and very severe, affecting his self-control and leading to "blackouts" and lapses of memory. They were associated with redness and watering of the eye. There was no nausea, vomiting or visual disturbance, and the attacks were not apparently related to mental stress. General health was normal, and there was no history of head injury or other significant illness. Physical examination on many occasions showed no abnormality except for depression of the corneal reflex on the affected side. Full neurosurgical examinations were carried out in 1948, 1949 and 1950, including air studies and arteriograms, without demonstrating any abnormality. Temporal arterectomy was carried out in 1949 without benefit. Local anaesthesia induced in the region of the supraorbital, supratrochlear and auriculo-temporal nerves frequently relieved the pain. Section of the nerves was carried out in June, 1950, September, 1951, and June, 1952, with subsequent periods of relief up to six months. On February 4, 1953, Dr. Stuart Morson undertook section of the first division of the trigeminal nerve. He made the following operation note:

... by the Frazier approach the left trigeminal ganglion and root were exposed and the ophthalmic fibres cut. When these were cut it was observed that a spicule of bone was projecting up into the plexus triangularis of the ganglion just between the ophthalmic and maxillary divisions. It was possible to nip this off with pituitary rongeurs.

Dr. Reader said that the patient was now anaesthetic in the ophthalmic distribution of the trigeminal nerve, and the corneal reflex was lost on the left side. There had been no recurrence of the headache. He considered that it was too early to draw conclusions, but it seemed probable that symptoms had been due to mechanical irritation of the ganglion.

#### Thyrotoxicosis in a Child.

Dr. Reader's second patient was a girl who had been aged five years at the time of onset of symptoms. She had been in normal health until January, 1951, when, after an attack of *otitis media*, she suffered bouts of vomiting and frequency of defecation (five or six formed stools per day). At the same time she was irritable and cranky, though eating well and gaining weight. Thyrotoxicosis was diagnosed by Dr. R. D. Spooner, and she was referred to the Royal Prince Alfred Hospital out-patient department. The basal metabolic rate as determined by Dr. F. S. Hansman was +17%. At examination on May 16, 1951, she was found to be a small lively child, with a weight of two stone thirteen and a quarter pounds and a height of three feet six inches. She had obvious exophthalmos and lid lag and a soft diffuse enlargement of the thyroid gland. No thrill or bruit was detected, and no finger tremor was apparent. The pulse had a rate of 128 per minute and was regular. The blood pressure was 140 millimetres of mercury, systolic, and 80 millimetres, diastolic. On her admission to hospital in June, 1951, the physical signs were unchanged. The basal metabolic rate was +23%. Her condition was considered non-toxic, and she was discharged from hospital after one week.

In August, 1951, she developed an incipient thyroid crisis with vomiting for four days and diarrhoea for two; she had lost seven pounds in weight during the two months since her discharge from hospital and four pounds in one week. She was readmitted to hospital immediately and given

sedatives, and methyl thiouracil therapy was commenced. The tachycardia and raised systolic pressure persisted for some months in spite of a fall of basal metabolic rate to -23% and a slow but steady gain in weight. She was discharged from hospital in December, 1951, taking 100 milligrammes of methyl thiouracil daily.

Dr. Reader went on to say that in the subsequent eighteen months, treatment had been supervised in the out-patient department. In the early stages the patient developed obvious myxœdema with pale puffy face, very dry skin and constipation. A notable feature was prominence of the lower jaw. The exophthalmos increased, and the thyroid became larger. Subsequently the dosage of methyl thiouracil was varied from 12.5 to 25 milligrammes daily, according to the mother's assessment of the child's well-being, and that had improved steadily in recent months. In particular, the exophthalmos had entirely subsided. Methyl thiouracil therapy was suspended in March, 1953, after eighteen months' continuous administration.

Dr. Reader made the following comments on the case. First, the symptoms of thyroid toxicity throughout the course of the illness had been consistent and were irritability, vomiting and frequency of defecation. Second, the signs were tachycardia, raised systolic blood pressure and loss of weight; there was no finger tremor; exophthalmos and goitre were prominent, but were dissociated from the degree of thyrotoxicosis. Third, the basal metabolic rate seemed consistent with the clinical manifestations in spite of the difficulty of performing the test in a child. Fourth, initial control with methyl thiouracil was slow but, in the long run, successful. Fifth, although during the course of the illness weight changes seemed slight and of little significance, in a review of the data they appeared to have given a consistent indication of the effectiveness of therapy.

#### Ankylosing Spondylitis.

Dr. Reader's third patient was a woman, aged forty-two years, suffering from ankylosing spondylitis. The onset had been insidious in 1949, the patient then being aged thirty-nine years, with aching pain in the lower part of the back and thighs and also in the thoracic region, first noted during exertion such as playing golf. There was some lassitude but no frank toxæmia. Symptoms became steadily worse, stiffness of the back was noted after about a year, and aching was present all the time. She found it impossible to get comfortable in bed and to rest her head on the pillow. Investigation of the family history showed that there were 13 siblings, and of those one, a brother, now aged fifty-six years, suffered from very severe ankylosing spondylitis. A diagnosis of ankylosing spondylitis was made by Dr. D. Brennan early in 1951, and a course of deep X-ray therapy commenced at Lewisham Hospital. The treatment was given up because of attacks of fluttering in the chest suggesting paroxysmal tachycardia. A course of ultrasonic therapy was commenced at Royal Prince Alfred Hospital in September, 1951, and continued for six months. No definite improvement occurred, and in April, 1952, the patient had an acute exacerbation of pain. At that stage her entire spine was quite rigid, and extension and rotation of the neck were limited to about half the normal range. There was slight cervical kyphosis. She was unable to look directly upwards, but could just see the angle between the wall and ceiling when standing four feet back from the wall. Chest expansion was three-quarters of an inch. On forward-bending the hands reached to within 18 inches of the floor. A further course of deep X-ray therapy was commenced on May 14, 1952. It was proposed to give each area of the back six doses of 300r at daily intervals. No precautions were taken to protect the ovaries. Subjective improvement was definite after one week. She was able to lie comfortably in bed for the first time in months, and the pain was less severe. There was a progressive fall in the number of leucocytes (to 2000 per cubic millimetre) and the hæmoglobin value, and in the third week weakness, nausea and vomiting became troublesome. The last two applications were abandoned.

Dr. Reader said that subjective improvement had been maintained in the subsequent year, and slight but definite objective improvement had continued for several months after treatment and had been maintained. Menstrual function had been grossly disturbed, this being associated with hot flushes, but sterilization had not occurred. Periods of amenorrhœa up to three months had alternated with menorrhagia. Adjuvant therapy had consisted of breathing exercises, the use of a flat firm bed, ferrous sulphate and stilbœstrol for the hot flushes.

Dr. Reader made the following comments. First, the case was a typical, though rather rapidly progressive, example

of ankylosing spondylitis. Second, in the early stages the symptoms had been thought to be due to fibrositis or sciatica. Third, the condition was not uncommon in females, though the sex ratio was generally five males to one female. Fourth, the disease was frequently familial, especially when occurring in women. Fifth, the symptomatic response to X-ray therapy could be expected in all except advanced cases; but the dosage must be heavy, and leucopenia was usual.

#### Demonstration from Arthritis Clinic.

DR. SELWYN NELSON showed three patients from the arthritis clinic.

The first was a girl, aged eleven years, suffering from rheumatoid arthritis. Her case illustrated the long-term use of cortisone. She had been admitted to hospital at the age of nine years on December 19, 1951, complaining of pain in the feet for three weeks, soreness of the arms for two weeks, and soreness of the fingers for two days, associated with malaise, fever, loss of weight and a slight cough. On examination of the patient slight swelling of the hands was noted in the region of the metacarpo-phalangeal joints, with tenderness in these regions and in the metatarso-phalangeal regions of both feet. There was no limitation of movement at any joint. The temperature was raised (101° F.). She was rather pale. Nutrition was good. A blood count revealed 3,630,000 erythrocytes per cubic millimetre, 6200 leucocytes per cubic millimetre with a normal differential count, a hæmoglobin value of 9.7 grammes per centum, and an erythrocyte sedimentation rate of 17 millimetres in the hour. Cortisone therapy was commenced on December 22, 1951, by intramuscular injection, the initial dose being 100 milligrammes and the daily dosage 75 milligrammes. This was continued until January 17, 1952, when three 25-milligramme tablets a day were given instead of the single injection of the suspension. Thereafter the dose was reduced as clinical improvement permitted by steps of 12.5 milligrammes, with occasional increases of dosage when an exacerbation caused temporary increase in pain. At the time of her discharge from hospital on November 21, 1952, she was taking 37.5 milligrammes a day. That was further reduced to 25 milligrammes daily, but in May, 1953, was increased again to 75 milligrammes a day on account of further signs of activity of the disease. The side-effects noted were slight "moon face" and abdominal striae. At no time was any œdema noted. The blood pressure showed no tendency to increase. The doses given were not sufficient to control fully the damage to joints, and involvement of the left hip occurred resulting in limitation of flexion to 50°. The wrists also became painful, and a tendency to flexion deformity had to be countered by the use of cock-up splints worn at night. At the present time there was slight limitation of movement of the cervical part of the spine and slight periarticular swelling of both knees with 5° loss of full extension.

During her hospital stay she had repeated attacks of pyelitis, the organisms being *Bacillus coli*, *Streptococcus faecalis* and *Bacillus pyocyaneus*. They were treated by appropriate antibiotics after sensitivity tests; penicillin, streptomycin, aureomycin, chloramphenicol and terramycin all were used at various times. The erythrocyte sedimentation rate remained on the whole high, but was down to 11 millimetres in the hour at the time of her discharge from hospital. In addition to cortisone she received "Myocrisin" 0.02 gramme weekly commencing on January 17, 1952. Salicylates and analgesics were given throughout. She had the advantage of occupational therapy and did correspondence lessons during her stay in hospital to such good purpose that on resuming school attendance she was able to come top of her class in recent examinations.

Dr. Nelson said that it was felt that the use of cortisone in her case, while not affecting the underlying disease, had reduced the damage to her joints to a minimum. Similar patients who did not have such therapy usually progressed fairly rapidly to crippling deformity, often with complete ankylosis at various joints. The dosage was a compromise between that which would give full control of the disease with the accompaniment of undesirable side-effects, and that which, while producing no such side-effects, was nevertheless insufficient to protect the joints. Cessation of the treatment before the subsidence of the underlying rheumatoid process would allow the joint damage to proceed unchecked and undo any good derived from the previous therapy.

The second patient was a man, aged sixty-seven years, with a two years' history of swelling of the hands and wrists. For fifteen years he had noted lumps in the vicinity of both elbows. He had no history of episodes of acute arthritis of the type usually met with in gout, and no family history of gout. The nodules on elbows, forearms

and hands were typical of rheumatoid arthritis. Swelling and tenderness were present in the region of the metacarpophalangeal joints and proximal interphalangeal joints. Clinically the patient suffered from active rheumatoid arthritis. X-ray examination of the hands showed very extensive "cystic" destruction in the vicinity of the joints of the hand with much erosion of articular surfaces of many sites; it involved the carpus, metacarpophalangeal joints and proximal interphalangeal joints, with sparing of the distal interphalangeal joints. There was little loss of articular cartilage or disturbance of alignment. A trial of colchicine therapy produced no improvement, but improvement followed the use of gold. Dr. Nelson said that the patient was presented to illustrate the occurrence in rheumatoid arthritis of radiographic changes suggesting gout.

The third patient was a man, aged twenty-seven years, suffering from ankylosing spondylitis. It had commenced at the age of sixteen years, and when the patient was first examined at the arthritis clinic he had already been treated by deep X-ray therapy to the sacro-iliac joints and lumbar, thoracic and cervical parts of the spine. The sacro-iliac joints were ankylosed, and the spine was rigid, but in fairly good position. The complaint at his examination in June, 1950, was of severe pain in the left hip joint and in the right shoulder. Attempted passive movement of the left leg provoked excruciating pain. Deep X-ray therapy to the left hip and right shoulder, followed by painstaking reeducation by the physiotherapist, resulted in complete subsidence of the arthritic process and satisfactory rehabilitation.

(To be continued.)

## Out of the Past.

*In this column will be published from time to time extracts, taken from medical journals, newspapers, official and historical records, diaries and so on, dealing with events connected with the early medical history of Australia.*

### INJURIES FROM CATTLE DYING WITH THE BLACK-LEG.

[*The Sydney Morning Herald*, December 14, 1850.]

Two labouring men named Fishway and Dickens are now lying in a very precarious state of health at Concord from the following cause:

It appears a beast had died in the bush and the parties for the sake of feeding their dogs, had cut and taken away a portion of the carcase. After a short time their limbs began to swell and Drs. Rutter and Gwynne were sent for. The poor men still lie in a very dangerous state. Cases similar to the above have repeatedly taken place and surely call for some legislative consideration.

## Correspondence.

### ACUTE INFECTIONS OF THE FINGERS AND HAND.

SIR: I have read with a tolerant interest the correspondence in your recent numbers on infections of the hand; I also recently heard a lecture on the subject by a junior surgeon who has dealt with more than one hundred cases in a "Hand Clinic" in the past year. A few remarks may not be out of place, but I am determined not to enter into controversy on the subject.

The work of Kanavel has been derided because he taught, as we older men learned to our profit, that tendon-sheath infections at that time spread by them to the flexor sheaths below and above the transverse carpal ligament. He also taught, as we knew full well, that actual pus eroded its way out of the flexor tunnels—pus will erode bone; we have experienced cases in which both infection and pus have extended not only to the flexor compartment above the wrist but also more proximally in the forearm, requiring incisions and at times followed by gangrene of fingers and

part of the hand—often the result of ligations for secondary hæmorrhages. More, there was the odd case in which the arm became rapidly oedematous with a gravely ill patient, and pleural pain was rapidly followed by effusion and abdominal distension as the terminal features of a fatal septicæmia.

Then, as now, it was not always easy to determine when to incise for pus; there is no rule for this except clinical acumen and experience, which can also be fallacious. Anyone knows that a hot, red, brawny or fluctuating swelling calls for incision. It has been said that we "old-timers" incised pulp infections to let out "bad blood". Surely that was a mediæval practice, as I had not previously heard of it!

What I am driving at is this. The younger surgeons do not know of the amazingly beneficial change which has been brought about by the use of penicillin and the "sulpha" drugs. They have made infections of the hand "baby stuff"—pallid spectres of what we "old-fashioned surgeons" had to deal with, and with which work Kanavel was concerned.

As for the time to let out pus under latter-day conditions, the same therapeutic agents make it almost immaterial; it can safely be left till there is advanced local swelling, brawny or fluctuant. And whether part or the whole of the nail is removed in perionychia is likewise immaterial.

A small series of cases over a short period will teach little or nothing at all; I suspect all reported series—except my own!

Yours, etc.,

W. MAXWELL.

141 Macquarie Street,  
Sydney,  
October 26, 1953.

## Post-Graduate Work.

### THE MELBOURNE PERMANENT POST-GRADUATE COMMITTEE.

#### SUMMARY OF COURSES TO BE CONDUCTED IN MELBOURNE IN 1954.

The following schedule is published as a guide for those who may be planning post-graduate study in Melbourne in 1954.

#### Courses for Candidates for Higher Qualifications.

##### Part I Examinations.

Courses in the following subjects are suitable for candidates for Part I of the M.D., M.S., D.G.O., D.O., D.L.O., D.P.M., D.D.R., D.T.R., D.A., Primary F.R.A.C.S. and College of Radiologists examinations:

Anatomy. The course commences on March 1 and will be conducted on Monday and Wednesday afternoons for four or five months.

Physiology. The course commences on March 1 and will be conducted on Monday and Wednesday afternoons for four or five months.

Pathology. The course commences on March 15 and will be conducted on Monday and Wednesday afternoons for four or five months.

Physics. The course commences on March 4 and will be conducted on Thursday afternoons for eighteen weeks.

Psychology I. The course commences in March and will be conducted on a part-time basis for eight months.

##### Part II Examinations.

Courses for candidates for Part II examinations are as follows:

For M.D. and M.R.A.C.P. a course in medicine is to be arranged.

For M.S. and F.R.A.C.S. a course in surgery is to commence in the middle or end of February and run for about ten weeks on a full-time basis.

Basic courses for the diplomas. A course in bacteriology is to commence in June and continue on a part-time basis for ten or twelve weeks. A course in basic pathology is to commence on March 15 and continue on Monday and Wednesday afternoons for four months.

For D.D.R. and Part II of College of Radiologists examinations. Courses in radiodiagnosis and special pathology will

\* From the original in the Mitchell Library, Sydney.

commence in April or May and continue on a part-time basis for ten or twelve weeks.

For D.T.R. and Part II of College of Radiologists examinations. Courses in radiotherapy and physics will be arranged when sufficient numbers present.

For D.P.M. Course in psychiatry will commence in May or June on a part-time basis. Lectures will be arranged in neuropathology about the time the psychiatry course is in progress. A course in psychopathology is to run from March for eight months on a part-time basis.

For D.O. Ophthalmology and special pathology courses will commence early in June and continue on a part-time basis for three or four months.

For D.G.O. Gynaecology and obstetrics and special pathology courses will be arranged when sufficient numbers present.

#### Refresher Courses.

##### Gynaecology and Obstetrics for Young Graduates.

A gynaecology and obstetrics refresher course for young graduates will be conducted at the Women's Hospital on a full-time basis for two weeks commencing on February 1. Limited residence will be available at the hospital.

##### Pædiatrics in General Practice.

A course in common pædiatric conditions in general practice will be conducted at the Children's Hospital on a full-time basis for one week commencing on February 15.

##### Gynaecology and Obstetrics for General Practitioners.

A gynaecology and obstetrics refresher course for general practitioners will be conducted at the Women's Hospital on a full-time basis for two weeks, commencing July 5. Residence will be available at the hospital.

#### Further Announcements and Enrolments.

Announcements stating the organizations which will conduct these courses will be made at a later date. For all courses, except those in psychology I and psychopathology, enrolments should be made through the Melbourne Permanent Post-Graduate Committee, 394 Albert Street, East Melbourne. Telephone: FB 2547.

#### THE POST-GRADUATE COMMITTEE IN MEDICINE IN THE UNIVERSITY OF SYDNEY.

##### Course in Advanced Medicine.

THE Post-Graduate Committee in Medicine in the University of Sydney announces that a course in advanced medicine suitable for candidates for the examination for membership of The Royal Australasian College of Physicians will be held for a period of twelve weeks commencing January 11, 1954. The fee for attendance will be £31 10s. or £2 12s. 6d. per week. The programme has been arranged to take place in the afternoons from Monday to Friday and on Saturday mornings.

It is desirable that candidates should have had considerable experience in clinical work either in hospital or medical practice before considering themselves prepared to take examinations for higher medical degrees or diplomas. The course will also be found of value to practitioners intending to devote further time to acquiring such experience before taking the examination and to those who are not seeking higher qualifications, but who are anxious to widen their knowledge of internal medicine.

The scope of the course includes special instruction in electrocardiography, ward rounds and demonstrations of cases at the principal metropolitan hospitals, regular clinicopathological conferences, lecture-demonstrations in pathology, hæmatology and biochemistry, demonstrations of the application of radiological methods of diagnosis to medical diseases, tutorials in case-taking, demonstrations and lectures in pædiatrics, demonstrations and lectures in psychiatry, and demonstrations of neurological cases and electroencephalography.

The supervisor of the course will conduct tutorials on selected subjects and will be available to discuss with students any problems arising in the course. It is expected that students will devote considerable time to reading of text-books and current medical literature.

Fees are payable in advance at enrolment date, and early application is desirable. Applications to attend the whole or part of the course should be addressed to the Course Secretary, the Post-Graduate Committee in Medicine, 131 Macquarie Street, Sydney. Telephones: BU 5238, BW 7483.

DISEASES NOTIFIED IN EACH STATE AND TERRITORY OF AUSTRALIA FOR THE WEEK ENDED OCTOBER 3, 1953.<sup>1</sup>

Disease.	New South Wales.	Victoria.	Queensland.	South Australia.	Western Australia.	Tasmania.	Northern Territory.	Australian Capital Territory.	Australia.
Acute Rheumatism .. ..	8(5)	5(4)	..	..	..	..	..	..	13
Amoebiasis .. ..	..	..	..	..	..	..	..	..	..
Ancylostomiasis .. ..	..	..	1	..	..	..	1	..	2
Anthrax .. ..	..	..	..	..	..	..	..	..	..
Bilharziasis .. ..	..	..	..	..	..	..	..	..	..
Brucellosis .. ..	..	..	..	..	..	..	..	..	..
Cholera .. ..	..	..	..	..	..	..	..	..	..
Chorea (St. Vitus) .. ..	2	1(1)	..	..	..	..	..	..	3
Dengue .. ..	..	..	..	..	..	..	..	..	..
Diarrhoea (Infantile) .. ..	3(2)	4(3)	7(6)	..	..	..	4	..	18
Diphtheria .. ..	9(6)	3(1)	3(2)	..	2(2)	..	..	..	17
Dysentery (Bacillary) .. ..	..	1(1)	..	..	..	..	..	1	2
Encephalitis .. ..	..	..	..	..	..	..	..	..	..
Filariasis .. ..	..	..	..	..	..	..	..	..	..
Homologous Serum Jaundice .. ..	..	..	..	..	..	..	..	..	..
Hydatid .. ..	..	1(1)	..	..	..	..	..	..	1
Infective Hepatitis .. ..	..	13(11)	..	..	11(8)	..	..	..	24
Lead Poisoning .. ..	..	4(4)	..	..	..	..	..	..	4
Leprosy .. ..	..	..	..	..	..	..	..	..	..
Leptospirosis .. ..	..	..	..	..	..	..	..	..	..
Malaria .. ..	..	..	..	..	..	2	..	..	2
Meningococcal Infection .. ..	3(1)	4(3)	1(1)	..	1(1)	..	..	..	11
Ophthalmia .. ..	..	..	..	..	..	..	..	..	..
Ornithosis .. ..	..	..	..	..	..	..	..	..	..
Paratyphoid .. ..	..	..	..	..	..	..	..	..	..
Plague .. ..	..	..	..	..	..	..	..	..	..
Poliomyelitis .. ..	6(4)	..	..	5(4)	1	..	..	..	12
Puerperal Fever .. ..	..	..	1(1)	..	..	..	..	..	1
Rubella .. ..	..	13(9)	1	..	21(17)	..	..	..	35
Salmonella Infection .. ..	..	..	..	..	..	..	..	..	..
Scarlet Fever .. ..	9(4)	28(21)	24(21)	..	..	..	..	..	61
Smallpox .. ..	..	..	..	..	..	..	..	..	..
Tetanus .. ..	..	..	1(1)	..	..	..	..	..	1
Trachoma .. ..	..	..	..	..	..	..	..	..	..
Trichinosis .. ..	..	..	..	..	..	..	..	..	..
Tuberculosis .. ..	28(17)	25(22)	8(6)	9(5)	7(6)	3	..	..	78
Typhoid Fever .. ..	5(3)	2(1)	..	..	..	..	..	..	7
Typhus (Flea, Mite- and Tick-borne) .. ..	..	..	..	..	..	..	..	..	..
Typhus (Louse-borne) .. ..	..	..	..	..	..	..	..	..	..
Yellow Fever .. ..	..	..	..	..	..	..	..	..	..

<sup>1</sup> Figures in parentheses are those for the metropolitan area.

## University Intelligence.

### THE UNIVERSITY OF MELBOURNE.

#### University Elections, 1953.

AN election is to be held on Monday, November 30, 1953, to determine the five representatives of graduates on the Council of the University of Melbourne. There are nine candidates. The five elected will hold office until December, 1957.

Applications by graduates for voting papers may be made to the Returning Officer (Mr. F. H. Johnston) in writing not later than Friday, November 20, when the necessary material will be sent by post.

The candidates are as follows:

Dr. Lucy Meredith Bryce.<sup>1</sup> Nominated by Mr. Justice Dean and Mr. R. W. T. Cowan.

John Gurner Burnell.<sup>1</sup> Nominated by Mr. Justice Dean and Professor A. R. Chisholm.

Dr. Albert Ernest Coates. Nominated by Mr. W. E. A. Hughes Jones and Dr. Geoffrey Penington.

The Honourable Mr. Justice Arthur Dean.<sup>1</sup> Nominated by Professor A. R. Chisholm and Dr. C. H. Fitts.

Dr. Clive Hamilton Fitts.<sup>1</sup> Nominated by Sir John Newman Morris and Sir Russell Grimwade.

The Honourable Sir Edmund Francis Herring.<sup>1</sup> Nominated by Professor A. R. Chisholm and Mr. Justice Dean.

Sir Peter MacCallum. Nominated by Sir Wilberforce Newton and Sir Victor Hurley.

Alexander McDonell. Nominated by Mr. H. G. Henry and Mr. E. B. Pederick.

Dr. Edward Rowden White. Nominated by Sir John Newman Morris and Dr. A. E. Rowden White.

## Naval, Military and Air Force.

### APPOINTMENTS.

THE following appointments, changes *et cetera* have been promulgated in the *Commonwealth of Australia Gazette*. Number 64, of October 22, 1953.

#### AUSTRALIAN MILITARY FORCES.

##### Australian Regular Army.

*Royal Australian Army Medical Corps (Medical).*

3/40123 Captain (Temporary Major) A. P. Hanway is appointed from the Regular Army Special Reserve with a Short Service Commission for a period of one year, and to be Captain and Temporary Major, 1st October, 1953.

##### Citizen Military Forces.

*Northern Command: First Military District.*

*Royal Australian Army Medical Corps (Medical).*—The following officers are appointed from the Reserve of Officers, and to be Captains (provisionally): Honorary Captains 1/39148 F. Schubert, 11th August, 1953, and 1/39164 I. R. Ferguson, 18th August, 1953.

*Eastern Command: Second Military District.*

*Royal Australian Army Medical Corps (Medical).*—To be Temporary Major, 24th August, 1953: 2/115677 Captain M. T. Havyatt.

*Southern Command: Third Military District.*

*Royal Australian Army Medical Corps (Medical).*—The following officers are appointed from the Reserve of Officers, and to be Captains (provisionally): Honorary Captains 3/52296 I. N. Nunn and 3/101820 P. Ebeling, 27th July, 1953, and 3/101826 L. K. Morgan, 30th July, 1953. To be Captain (provisionally), 27th August, 1953: 3/101024 George Randall Stirling.

##### Reserve Citizen Military Forces.

*Royal Australian Army Medical Corps (Medical).*

*2nd Military District.*—The resignation of Captain J. L. Taylor, M.C., of his commission is accepted, 3rd August, 1953.

<sup>1</sup> Retiring candidates.

Major J. R. Radcliff is retired, 16th July, 1953. To be Honorary Captains: Arthur Douglas Spears, 3rd August, 1953, Kenneth Halford Mackey, 16th August, 1953, Bernard Greer, 17th August, 1953, Keith Patrick William Moore, 23rd August, 1953, John Daniel Cashman, 1st September, 1953, and Ross Arthur Johnson, 2nd September, 1953.

*4th Military District.*—Major A. A. Abbie is placed upon the retired list (4th Military District) with permission to retain his rank and wear the prescribed uniform, 3rd August, 1953.

## Medical Appointments.

Dr. R. G. Gold has been appointed medical registrar at the Royal Adelaide Hospital.

Dr. P. M. Last has been appointed out-patients' registrar at the Royal Adelaide Hospital.

## Diary for the Month.

Nov. 10.—New South Wales Branch, B.M.A.: Executive and Finance Committee.

Nov. 11.—Victorian Branch, B.M.A.: Clinical Meeting.

Nov. 14.—Victorian Branch, B.M.A.: Country Branch Meeting.

Nov. 16.—Victorian Branch, B.M.A.: Finance Subcommittee.

## Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

*New South Wales Branch* (Medical Secretary, 135 Macquarie Street, Sydney): All contract practice appointments in New South Wales.

*Victorian Branch* (Honorary Secretary, Medical Society Hall, East Melbourne): Associated Medical Services Limited; all Institutes or Medical Dispensaries; Australian Prudential Association, Proprietary, Limited; Federal Mutual Medical Benefit Society; Mutual National Provident Club; National Provident Association; Hospital or other appointments outside Victoria.

*Queensland Branch* (Honorary Secretary, B.M.A. House, 225 Wickham Terrace, Brisbane, B17): Brisbane Associated Friendly Societies' Medical Institute; Bundaberg Medical Institute. Members accepting LODGE appointments and those desiring to accept appointments to any COUNTRY HOSPITAL or position outside Australia are advised, in their own interests, to submit a copy of their Agreement to the Council before signing.

*South Australian Branch* (Honorary Secretary, 178 North Terrace, Adelaide): All Contract Practice appointments in South Australia.

*Western Australian Branch* (Honorary Secretary, 205 Saint George's Terrace, Perth): Norseman Hospital; all Contract Practice appointments in Western Australia. All government appointments with the exception of those of the Department of Public Health.

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